Volume 7 **Neurology** *Number 10*

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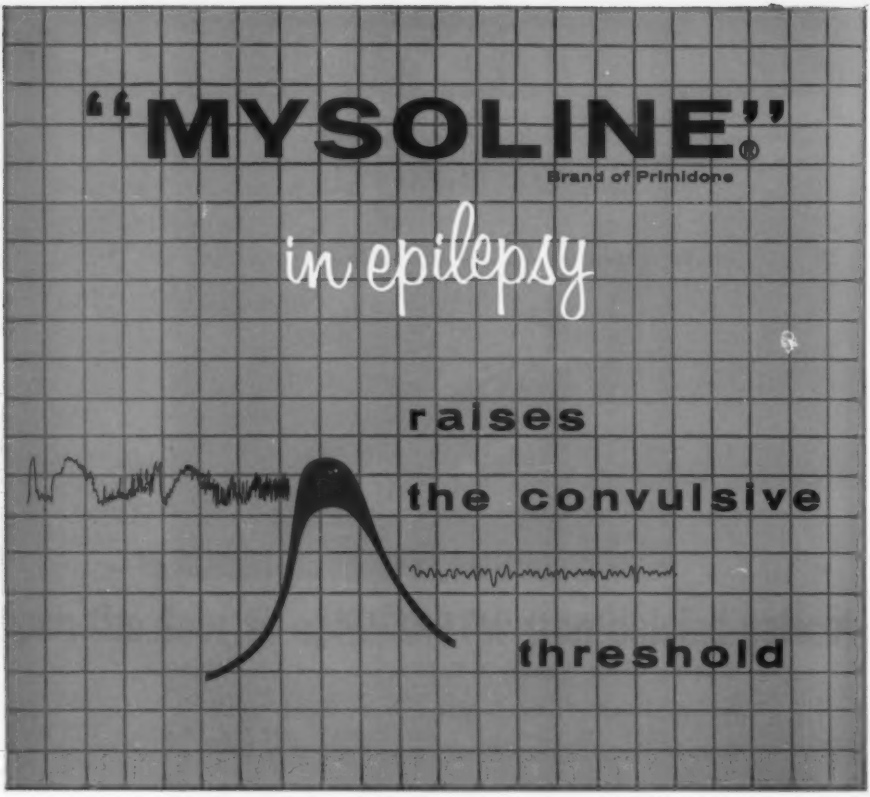

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NOVEMBER 1957 • *Contents*

Poliomyelitis
16. A Study of Pulmonary Edema 743
A. B. BAKER, M.D.

Reading Epilepsy 752
A. BINGEL, M.D.

Observations Upon Responses to Digital Carotid Artery Compression in Hemiplegic or Hemiparetic Patients 757
J. E. WEBSTER, M.D. AND F. S. GURDJIAN, M.D.

Dispersion of Fluid Materials in Intracerebral Injections
General Observations in Conjunction with Injection Lobotomy and Chemopallidectomy 763
E. M. HOUSEPIAN, M.D. AND M. GUZMAN-LOPEZ, M.D.

Electroencephalographic Evaluation of Treatment in Obstructive Disease of the Basilar and Carotid Arteries 765
JOHN S. MEYER, M.D., WALTER WEGNER, M.D., CHARLES A. KANE, M.D. AND OSCAR M. REINMUTH, M.D.

A Clinical Study of 100 Aphasic Patients
1. Observations on Lateralization and Localization of Lesions 777
JOE R. BROWN, M.D. AND JOSEPHINE SIMONSON, M.A.

Spirodon (Tetrantoin): A New Anticonvulsant of the Hydantoin Group 784
TRACY J. PUTNAM, M.D. AND JOHN JACOBS, M.D.

(Continued on next page)

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Contents — *Continued*

Hydatid Cyst of the Brain and Its Treatment 789
B. GRIPONISSIOTIS, M.D.

Neurologic Diagnosis of Pancreatic Islet Cell Adenomas with Hyperinsulinism 793
J. C. RICHARDSON, M.D. AND F. M. HILL, M.D.

Case Reports

Tuberculoid Leprosy 798
THOMAS B. SUMMERS, M.D. AND GEORGE R. ZIMMERMAN, M.D.

Optic Atrophy as an Isolated Sign of Unruptured Carotid Aneurysm 803
LOWELL E. WHITE, JR., M.D. AND ELDON L. FOLTZ, M.D.

Intrinsic Glomerate Astrocytoma of the Cerebral Hemisphere in a Four Year Old Child 806
AXEL K. OLSEN, M.D. AND BLUITT L. LANDERS, JR., M.D.

Book Reviews 809

INFORMATION FOR *Authors*

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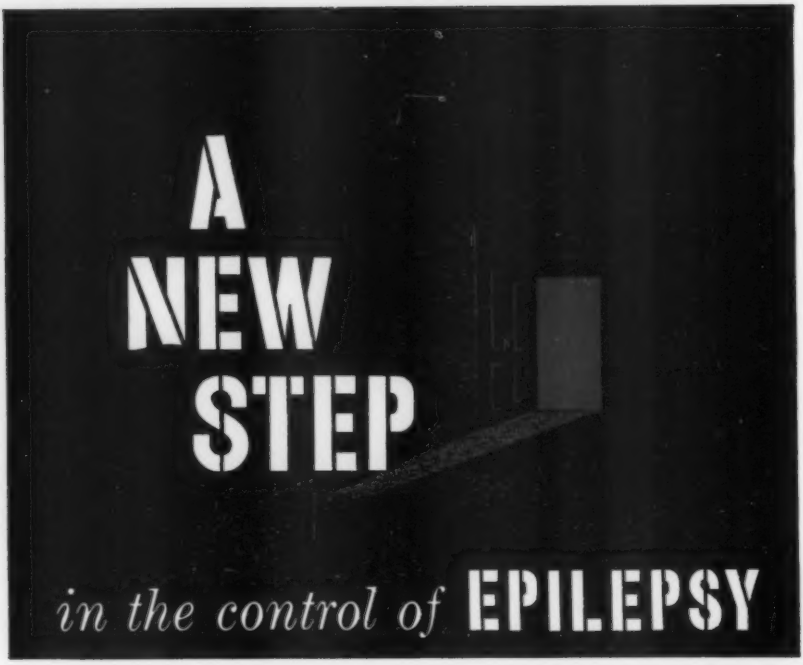

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In 1 series of 55 hospitalized psychotic patients treated with Vesprin, marked to moderate improvement occurred in approximately 66 per cent.

Five patients were discharged from the hospital. Two of these patients had not responded to any previous treatment.

In another small series of patients, which included 12 disturbed children, some improvement was seen in 11 of the 12 children who were treated with Vesprin for at least 2 months. In none of the children were any significant side effects observed.

In a third series of 123 psychotic patients treated with Vesprin for more than 3 months, 5 recovered from all of their active psychotic manifestations, particularly delusions and hallucinations, and 24 recovered from most psychotic manifestations with good social remission. An additional 78 patients showed significant improvement in their psychotic behavior.

Another group of schizophrenic patients has been treated with Vesprin for periods ranging from 6 months to 1 year. During this time clinical laboratory studies were made weekly, and later monthly, on urine and blood of the patients.

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- **Convulsions...not observed**

studies gave no evidence of drug toxicity.
Another investigator thought that Vesprin appeared to be more active and rapid in effect. The best response to Vesprin was seen in overactive, troublesome schizophrenic patients.

WHAT ARE THE ADVANTAGES? Clinical experience in hundreds of patients has shown that Vesprin does not oversedate the patient into sleepiness, drowsiness and lethargy. Drug-induced agitation is minimal.
Vesprin is active and rapid in controlling manic states, excitement and panic, and also in controlling the disturbing effects of delusions and hallucinations. Vesprin moderates hostile behavior and facilitates insight.
With Vesprin, intractable behavior patterns are rapidly brought under control. Thus, patients are made accessible to psychotherapy. Nursing care is reduced, and the patients' social rehabilitation is facilitated.
Extensive clinical experience has shown Vesprin to be singularly free from toxicity. Clinicians who have worked with the drug over long periods have not seen jaundice or liver damage, blood dyscrasias, or convulsions. Skin eruptions, photosensitivity or hyperthermia have been rarely observed.

WHAT ARE THE SIDE EFFECTS? Investigators have reported such symptoms as dizziness, nausea, weakness, drowsiness and epigastric distress in patients treated with Vesprin. Postural hypotension has been seen occasionally in normotensive patients. A hypotensive effect has been observed in patients with high blood pressure.
Anxiety and restlessness have been observed in some patients, and gain in weight in a few. These effects have usually been mild, and, as a rule have disappeared when the dosage was reduced or treatment stopped.
The most commonly encountered side effect has been the development of a Parkinson-like syndrome with motor disturbances and extrapyramidal symptoms. This syndrome is reversible and symptoms usually subside with a reduction of dosage or discontinuance of medication for 2 or 3 days.

VESPRIN

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WHEN IS IT INDICATED? Vesprin is indicated in treatment of various acute and chronic psychoses. Because it ameliorates psychomotor hyperactivity and assaultive behavior, Vesprin is particularly useful in management of schizophrenia, manic states, sociopathic personality disturbances with psychotic reactions, mental deficiency with psychoses, and psychoses associated with organic brain disease and senility.
Contraindications: Vesprin is contraindicated in comatose states due to central nervous system depressants (alcohol, barbiturates, opiates).

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Caution: Although no deleterious effects on the hemopoietic system have occurred to date in the extensive clinical use of Vesprin, routine blood counts are suggested during the course of therapy.
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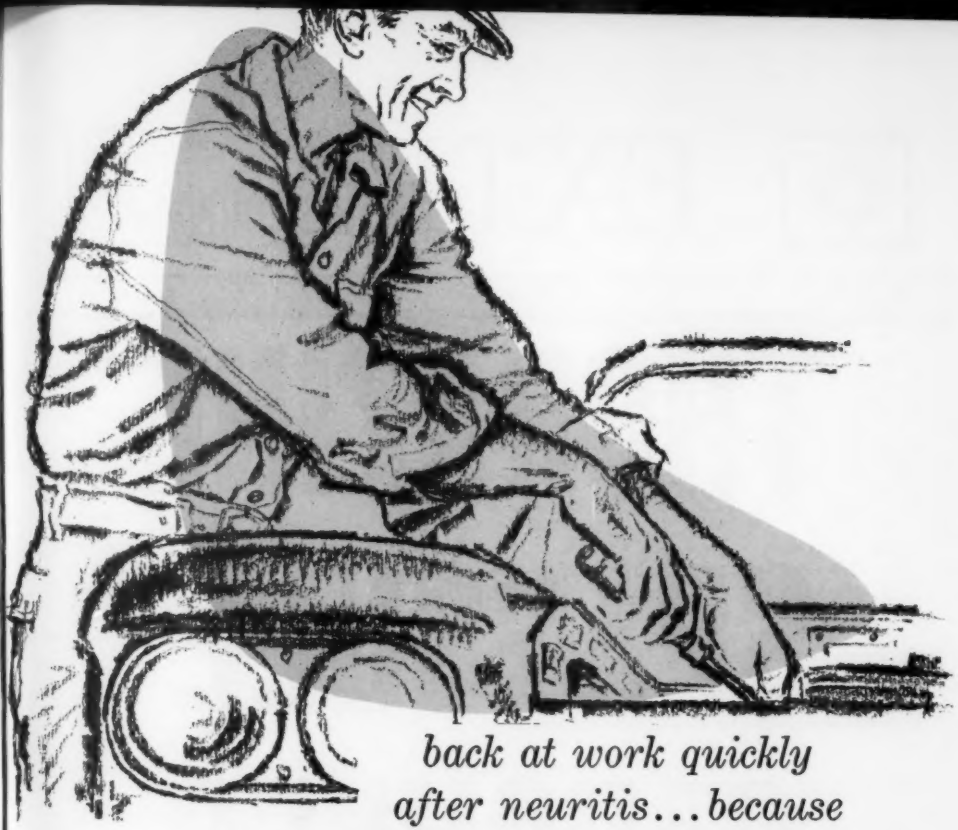

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Neurology Volume 7 • Number 11

Poliomyelitis

16. A Study of Pulmonary Edema

A. B. Baker, M.D.

One of the most disturbing complications of bulbar poliomyelitis is the sudden appearance of pulmonary edema, which often resists all forms of treatment and frequently produces the death of the patient. This complication often occurs suddenly, even in the presence of an illness that appears to be controlled or even subsiding. To date, the exact etiology of such pulmonary edema has escaped all forms of investigation. The fact that neural mechanisms are implicated cannot be avoided, since a similar complication has been observed in many other disturbances involving the central nervous system, such as brain tumors,[1] epilepsy,[1] cerebral hemorrhage, embolism, and thrombosis,[2,3] head injury, [4–6] and encephalitis.[7] In view of the importance of this complication to the welfare of the patient, it is not surprising that a great deal of investigative work has been undertaken in an attempt to elucidate the neural factors involved.

Since the vagus nerves were known to play an important role in both pulmonary vascular tone and cardiac function, it is not surprising that the earlier studies centered around the effects of bilateral vagotomy. Vieussens[8] apparently was the first to report lung changes after vagotomy. Legallois[9] in 1812 suggested that laryngeal denervation was the causative factor in lung edema and not the central impairment of pulmonary and cardiac function. There soon developed two distinct schools of thought. The one considered that bilateral vagotomy produced a primary disturbance in function of the pulmonary vessels and in cardiac function, thus resulting in pulmonary edema.[10–12] Farber[11] in a series of investigations showed that bilateral section of the recurrent laryngeal nerves alone did not result in pulmonary edema, in spite of possible obstruction, providing the airway was kept clean. However, bilateral cervical vagotomy often did result in pulmonary changes, particularly if the animal was given large amounts of fluid. Farber felt that the pulmonary changes were due to 1) loss of parasympathetic vasoconstrictors which deprives the pulmonary vessels of mechanisms necessary in adjustment of pulmonary vascular dynamics, and 2) changes in control of heart function due to its parasympathetic denervation.

The second school, which is most popular today, felt that all pulmonary changes which follow bilateral vagotomy may be due to a primary disturbance of laryngeal function with obstruction.[13–15] At the present time, it is felt that the major factor in vagotomy lung edema is airway obstruction and, if the airway can be kept clean and open, edema will not result.[16]

A number of investigators have attempted to produce pulmonary edema by direct irritation of the medullary centers. Jarish and his associates,[17] as well as Horst and his co-workers,[18] produced pulmonary changes in dogs, rabbits, and guinea pigs by injecting an irritant, Veratrin, into the cisterna magna. These investigators believed that Veratrin caused a sympathetic stimulation and, therefore, a vasopressor effect, thus forcing blood from the greater to the lesser circulation. This is accompanied by a concomitant loss of tone and an overdistention of the small pulmonary vessels.

Cameron and De[19] produced massive lethal pulmonary edema in rabbits by injecting a combination of fibrin and fibrinogen into the cisterna magna. They felt that the pulmonary

From the division of neurology, University of Minnesota School of Medicine, Minneapolis, Minnesota.

Read at the ninth annual meeting of the American Academy of Neurology, Boston, Massachusetts, April 25, 1957.

changes occurred as a result of vagal disturbance, with a resulting increase in pulmonary capillary permeability. Sarnoff and Sarnoff[20] repeated these experiments using dogs. They believed that fibrin resulted in an irritation of the sympathetic centers of the medulla, with stimulation of the cardiovascular centers producing an elevation of pulmonary and systemic arterial and venous pressures.

Gamble and Patton[21] were able to produce fatal hemorrhagic pulmonary edema in adult rats by discrete electrolytic lesions of the rostral hypothalamus in the region of the preoptic nuclei. In a few animals, more caudally placed lesions in the midline destroying the periventricular system produced edema.

The fact that the sudden onset of intracranial hemorrhage with an associated increased intracranial pressure often results in pulmonary edema[22] has led a number of investigators to study this factor of altered intracranial dynamics. Campbell and Visscher[23] subjected guinea pigs to increased intracranial pressure by injection of air into a rubber balloon placed extradurally. In these animals only a very mild pulmonary edema and congestion developed. Harrison and Liebow[24] produced intracranial pressure by introduction of Tyrodes solution subdurally in dogs. Tracheotomy was performed prior to the experiment. With the rise of intracranial pressure, there resulted a rise of left atrial pressure which was also associated with a rise of pulmonary capillary pressure, thus establishing conditions favorable for the development of pulmonary edema. Actual pulmonary edema occurred only in an occasional dog.

In view of the many different opinions regarding the neural mechanisms involved in pulmonary edema, it was felt that some further knowledge might be gained concerning this subject by a careful study of the central nervous system in a series of cases of pulmonary edema. During the period 1946 to 1951 the entire nervous system of over 150 patients dying of bulbar poliomyelitis became available for study. The case histories and the autopsy findings were checked carefully for cases which might be used for this study. Only those cases were selected in which both lungs showed extensive pulmonary edema on histologic study and weighed around 500 gm. or more. It was felt that the bilaterality of the lesions would facilitate histologic interpretation of the neurologic lesions. Using these rigid criteria, ten cases were available that could be considered as obvious cases of extensive bilateral pulmonary edema. In addition to the above, the autopsy records were also surveyed for cases which had no evidence of pulmonary changes and could be used as controls. Five cases were found in which bulbar poliomyelitis had terminated fatally but still the lungs showed no pathologic alterations and weighed under 200 gm. Since detailed studies of all areas of the nervous system had already been made and reported,[25–29] sections prepared with Nissl stain, hematoxylin-eosin stain, and Weil's stain were readily available from all areas of the nervous system in each of these 15 cases. The sections were carefully reviewed and the nature and degree of changes noted and tabulated in all areas of the brainstem, hypothalamus, and cerebral hemispheres. It was hoped that such a survey would enable us to compare the severity of lesions within the nervous system and to determine any differences in the pattern of lesions between fatal cases with pulmonary edema and those without lung changes.

A brief clinical survey of the clinical cases used in this study is given in order to facilitate the clinical pathologic correlation. The weight and histologic appearance of the lungs are included.

Case 1. A 46 year old man had a two-day history of malaise, headache, and beginning dyspnea. On admission to the hospital, the patient was apprehensive and dyspneic. His course was rapidly downhill and he expired within 32 hours. At autopsy the right lung weighed 900 gm. and the left 650 gm. In both lungs the alveoli were filled with transudate and some macrophages and erythrocytes (figure 1). The nervous system showed changes characteristic of poliomyelitis.

Case 2. A 17 year old boy developed headache, backache, and stiff neck shortly before admission. Two days later his respirations became shallow and rapid and he developed paresis of all limbs. His course was rapidly downhill, with the development of almost complete paralysis of all respiratory muscles, dysphagia, and restlessness. In spite of all procedures, he continued to go downhill and died three days later. The lungs at autopsy showed an extreme degree of hemorrhagic edema, the right lung weighing 770 gm. and the left 970 gm. The nervous system revealed extensive changes characteristic of poliomyelitis.

Case 3. A 34 year old man developed mild headache, malaise, and nuchal rigidity. When admitted to the hospital he showed weakness of both arms and dyspnea. A tracheotomy was performed. The patient was maintained for six days when he suddenly developed increasing dyspnea and expired. Both lungs on examination were very heavy and showed extensive hemorrhagic edema. The right lung weighed 1,325 gm. and the left 1,150

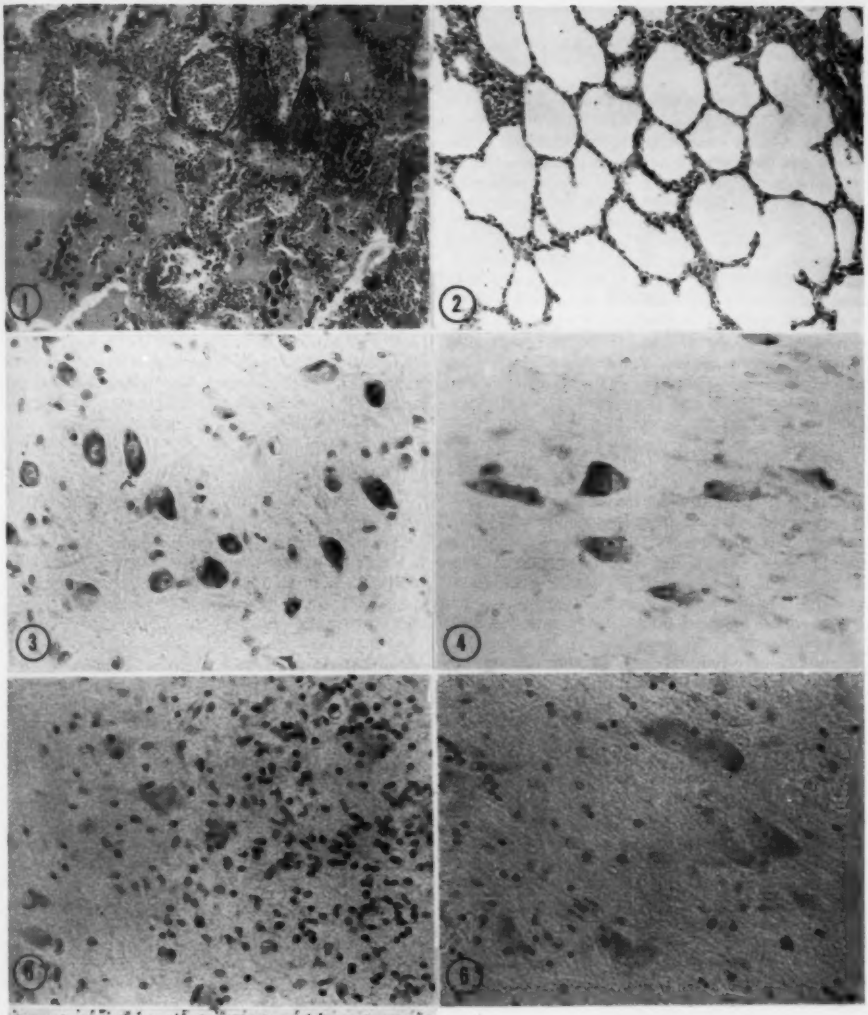

FIG. 1. Section of lung from a 46 year old man with fatal poliomyelitis. Lung weighed 900 gm. The alveoli are filled with homogeneous transudate, a few macrophages, and some erythrocytes.

FIG. 2. A 13 year old boy with fatal poliomyelitis. Lung weighed 165 gm. Alveoli are clear.

FIG. 3. Normal cells of the dorsal motor nucleus of the vagus in a patient with bulbar poliomyelitis without pulmonary edema. The Nissl granules are fairly coarse and tend to be distributed peripherally.

FIG. 4. Normal cells of the medial reticular substance of the medulla in a patient with bulbar poliomyelitis but without pulmonary changes. Nissl substance is finely granular and diffusely distributed throughout the cell body.

FIG. 5. Marked round-cell infiltration within the dorsal motor nucleus of the vagus. Many of the nerve cells are completely destroyed. Those still visible have lost most of their staining properties.

FIG. 6. Medial reticular cells of the medulla in a patient with pulmonary edema. The cells are markedly swollen and chromatolytic. Some fragmentation has occurred.

FIG. 7. Medial reticular cells of the pons in a patient with pulmonary edema. There are marked inflammatory changes replacing most of the tissue with destruction of the nerve cells.

gm. The brain and spinal cord showed the typical changes of poliomyelitis.

Case 4. A 39 year old man was admitted to the hospital with a six-day history of headache, vomiting, dysphagia, and beginning dyspnea. His clinical course was rapidly downhill and he expired within 24 hours of his admission. Pathologically, the lungs exuded a hemorrhagic edematous fluid on section. The right lung weighed 940 gm. and the left 630 gm. Study of the nervous system substantiated the diagnosis of poliomyelitis.

Case 5. A 34 year old man had a three-day history of nausea, restlessness, fever, and stiff neck. When first seen he had slight dysphagia but no dyspnea. He soon developed diaphragmatic and intercostal paralysis and was placed in a respirator. He continued to get worse and died three days after admission to the hospital. Examination of the lungs showed very extensive hemorrhagic pulmonary edema. The right lung weighed 1,140 gm. and the left 620 gm. The nervous system showed the characteristic tissue changes of poliomyelitis.

Case 6. A 27 year old man had a one-day history of fever, malaise, and dysphagia. Shortly after admission to the hospital he became unable to swallow even fluids and a tracheotomy was done. His condition showed no improvement. He soon went into shock and expired the day of admission. At autopsy both lungs were filled with a pale pink homogeneous material. The right lung weighed 1,025 gm. and the left 870 gm. The nervous system revealed the characteristic changes of poliomyelitis.

Case 7. A 34 year old man was admitted to the hospital because of vomiting and dysphagia for one day. During the next few days dysphagia increased and a tracheotomy was done. The patient appeared to be doing fairly well when he suddenly became cyanotic and expired. At autopsy the right lung weighed 520 gm. and the left 460 gm. Both lungs revealed extensive edema on microscopic section. The nervous system showed changes characteristic of poliomyelitis.

Case 8. A 30 year old man first noticed weakness of the legs five days after an upper respiratory infection. The following day he had difficulty in respiration and was placed in a respirator. Within 24 hours he went into shock and failed to respond to any treatment procedures. At autopsy the right lung weighed 520 gm. and the left 500 gm. Both revealed marked areas of edema. The nervous system showed the acute alterations of poliomyelitis.

Case 9. A 28 year old man had a one-day history of fever, stiff neck, and restlessness. During the next few days the patient got along well and then suddenly developed respiratory difficulty and weakness of the legs. His course continued rapidly downhill, cyanosis appeared and the patient expired on the fourth hospital day. At autopsy the right lung weighed 480 gm. and the left 510 gm. Both lungs showed large amounts of frothy bloody material on cut section. The nervous system revealed the typical changes of poliomyelitis.

Case 10. A 33 year old man was seen because of paresis of the left arm and difficulty in breathing. His hospital course was rapidly downhill. He showed progressive weakness of all muscles, increasing dyspnea, and finally rapid cyanosis and death two days after admission. At autopsy the right lung weighed 1,200 gm. and the left 610 gm. On cut surface abundant blood tinged fluid exuded. The nervous system findings were consistent with a diagnosis of poliomyelitis.

Case 11. A three and one half year old boy was admitted to the hospital after ten days of fever and sore throat. On admission there was marked dysphagia and nasal speech. Tracheotomy was done. The child seemed to improve but on the sixth day he suddenly developed marked dyspnea and expired. The lungs at autopsy showed scattered areas of atelectasis. The right lung weighed 120 gm. and the left 120 gm. The nervous system revealed typical changes of poliomyelitis.

Case 12. A ten year old boy was admitted to the hospial because of vomiting, stiff neck, and difficulty in breathing. A tracheotomy was performed and the patient appeared to improve. However, within a few hours he became cyanotic and expired. The lungs on examination showed no edema, the right weighing 180 gm. and the left 170 gm. The brain and spinal cord revealed extensive alterations consistent with a diagnosis of poliomyelitis.

Case 13. A 13 year old white boy was seen after a 12-day history of occipital headache, nausea, vomiting, and stiff neck. When seen in the hospital there was weakness of both arms and a slight nasal speech. The patient became restless and apprehensive and expired within 24 hours after entering the hospital. Examination of the lungs showed patchy areas of atelectasis, with the right lung weighing 185 gm. and the left 165 gm. (figure 2). The nervous system showed the typical changes of poliomyelitis.

Case 14. A four year old girl was admitted to the hospital because of headache, sore throat, and weakness of both legs. Shortly after admission she developed difficulty in breathing and was placed in a respirator. She got along fairly well until the eighth hospital day when she developed severe bulbar involvement and died. Pathologically, the lungs showed only scattered areas of increased consistency and some atelectasis. The right lung weighed 110 gm. and the left 130 gm. The nervous system revealed findings characteristic of poliomyelitis.

Case 15. A five year old girl was seen after three days of headache and fever. Shortly after admission to the hospital she developed dyspnea, dysphagia, and paresis of the limbs. The patient seemed to improve under treatment and apparently was gettting along well when she suddenly developed dyspnea and expired. At autopsy the right lung weighed 115 gm. and the left 90 gm. Both lungs showed areas of atelectasis and a few areas of bronchopneumonia. The nervous system revealed the typical changes of poliomyelitis.

PATHOLOGIC STUDIES

The histologic involvement in bulbar poliomyelitis consists of both diffuse interstitial-cell infiltration and neuronal damage. The nature and extent of these changes within the nervous system in poliomyelitis has already been described in great detail.[25–27] It might be well to review the normal structures in these areas in order to facilitate the description of the lesions observed.

Medulla

Normal structure. The principal nuclear groups studied were the nucleus ambiguus, the dorsal nucleus of the vagus, and the reticular cells. The cells of the nucleus ambiguus are identical with the somatic motor neurons found in the spinal cord and any histologic alteration is readily determined. Involvement of these cells results in difficulty in swallowing and talking.

The dorsal nucleus of the vagus is situated beneath the ala cinerea in the floor of the fourth ventricle. Its ventral border is placed between the nucleus of the tractus solitareous and the hypoglossal nucleus. It is composed of medium-sized cells with rather light-staining cytoplasm and small discrete and fairly dense Nissl bodies which have a peripheral arrangement within the cell (figure 3). Many of the cells are smaller and tend to be fusiform in outline. This nuclear structure supplies motor fibers to the palate, pharynx, larynx, trachea, bronchi, esophagus, and intestinal tract, and impulses which depress heart action. Involvement of these nuclei bilaterally should result in tachycardia, as well as perhaps some disturbance in bronchovascular tone.

The cells of the medullary reticular formation may be divided into two groups on the basis of size. The large cells are present in the ventromedial reticular formation. This nuclear group is about 14 mm. long, extending from 2 mm. caudal to the superior pole of the nucleus of the twelfth cranial nerve to the superior pole of the motor nucleus of the seventh cranial nerve in the pons. In the lower portion of the pons the cells are scattered between the midline and the seventh cranial nerve nucleus (figure 4). These cells apparently regulate circulation and their damage invariably produces clinical symptoms of vasomotor disturbance, such as irregular feeble pulse, low pulse pressure, fall of blood pressure, and terminal shock.[25]

The small reticular cells are present throughout the reticular formation of the medulla, chiefly in the lateral and dorsal areas. Only a few of these cells extend into the pons. These cells regulate respiratory function and their involvement causes irregular rhythm and depth of respiration, periods of apnea, and finally cessation of respiration.

Pathology. The histopathologic changes observed in the medulla of patients with and without pulmonary edema are listed in tables 1A and 1B. Two striking differences are at once apparent in comparing the tissue changes in these two groups. In all cases with pulmonary edema there was very extensive damage to both the dorsal nucleus of the vagus, as well as to the medial reticular cells within the medulla. In all these cases the dorsal nucleus of the vagus showed a marked inflammatory reaction of a focal and diffuse type with an associated destruction of the nerve cells (figure 5). The cell damage varied from 30 to 90 per cent. In most cases over half the cell elements were completely fragmented, with only remnants of the cell body still visible. Many of the remaining cells were swollen and chromatolytic. In contrast to this severe destruction were the minimal changes observed in those cases without pulmonary involvement (figure 3). Here the dorsal nucleus of the vagus showed very little alteration, with a maximum of 10 per cent of the nerve cells being altered (table 1B). Inflammatory changes were mild or entirely absent. The nerve cells were totally uninvolved in two of the cases, and in the others showed only mild swelling or early Nissl changes in scattered cells. The relative sparing of these nuclear groups in the cases without lung changes as compared to those cases with pulmonary edema was most striking.

Changes in the nucleus ambiguus did not differ in the two groups of cases. Although generally those cases with pulmonary edema revealed more intense alterations, some of these patients had as little as 5 per cent of the cells involved, while cases without pulmonary edema occasionally had as much as 25 per cent of the nucleus ambiguus damaged (tables 1A and 1B).

The cells of the medial reticular formation of the medulla showed a striking difference in the degree of damage in patients with pulmonary edema when compared to those without pulmonary changes. In the former, the cell damage was very severe in practically every case, the percentage of injured cells varying from 23 to 50 per cent. The cellular changes were very severe, consisting of cell fragmentation, cellular swelling, and nuclear damage

TABLE 1A

PERCENTAGE OF CELL DAMAGE IN MEDULLA IN CASES WITH PULMONARY EDEMA

Case No.	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.
Right dorsal nucleus of vagus	90	60	90	30	60	83	30	80	50	85
Left dorsal nucleus of vagus	50	50	50	50	30	30	30	70	40	40
Nucleus ambiguus	50	50		20	60	5	5	85	60	58
Medial reticular cells (vasomotor)	50	23	43	31	40	48	24	45	50	35
Lateral reticular cells (respiratory)	52	27	37	31	79	36	39	50	5	8

TABLE 1B

PERCENTAGE OF CELL DAMAGE IN MEDULLA IN CASES WITHOUT PULMONARY EDEMA

Case No.	11.	12.	13.	14.	15.
Right dorsal nucleus of vagus	0	5	10	5	0
Left dorsal nucleus of vagus	0	5	10	0	0
Nucleus ambiguus	0	5	25	5	0
Medial reticular cells (vasomotor)	14	0	0	28	32
Lateral reticular cells (respiratory)	27	58	25	37	25

(figure 6) (table 1A). In those cases without pulmonary edema two showed no alteration within this nuclear group, and in the remaining cases the changes were mild and consisted chiefly of some swelling of the cell body and tinctorial alteration (table 1B).

The lateral reticular cell group of the medulla revealed no differences in the degree of alteration between the two groups of patients. In both groups the cell changes were fairly extensive but rather inconsistent. In two cases with pulmonary edema this nuclear group showed almost no alterations, which would suggest that it probably plays little role in the problem of the pulmonary edema.

Pons

Normal structure. The principal nuclear groups within the pons consist of the motor nuclei of the fifth, sixth, and seventh cranial nerves, the reticular nuclei, and the tegmental nuclei. Only the reticular nuclei of the pons appear to be important to this study. The large cells of the ventromedial reticular formation are a continuation of the same cell group in the medulla and apparently play an important role in the regulation of circulation. The small cells of the lateral reticular nucleus are very few in number and apparently have little functional significance.

Pathology. In the pons there was again a very striking difference in the degree of cellular damage within the large medial reticular cells in patients with and without pulmonary edema. Those cases with pulmonary edema revealed very extensive and severe alterations within these cell elements. In all but one case at least 20 per cent of the cells were destroyed (figure 7) (table 2A). In the single case that showed only slight damage to this nuclear group, the caudal portion of this cell group within the medulla revealed 31 per cent of the cells injured. In those patients without pulmonary changes, the medial reticular cells of the pons showed very little alteration, and in three cases no involvement of any type was observed (table 2B).

The lateral reticular cells are confined chiefly to the medulla and very few extend into the pons. This nuclear group, therefore, appears to be relatively unimportant in the pons. The alteration within these cells showed no differences in degree or number between the two sets of patients.

Hypothalamus

The nuclear groups studied in this region of the brain consisted of the preoptic, supraoptic, paraventricular, and tuberal nuclei in the anterior hypothalamus; the dorsomedial, ventromedial, and lateral nuclei in the middle hypothalamus; and the posterior and mamillary nuclei in the posterior hypothalamus.

The neuronal changes in general consisted of acute swelling and diffuse or perinuclear chromatolysis. In cases of more severe involvement, the cell processes became fragmented and detached, leaving a rounded, swollen,

TABLE 2B

PERCENTAGE OF CELL DAMAGE IN PONS IN CASES WITHOUT PULMONARY EDEMA

Case No.	11.	12.	13.	14.	15.
Medial reticular cells (vasomotor)	10	0	0	5	0
Lateral reticular cells (respiratory)	80	12	25	30	80

TABLE 2A

PERCENTAGE OF CELL DAMAGE IN PONS IN CASES WITH PULMONARY EDEMA

Case No.	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.
Medial reticular cells (vasomotor)		30	25	3	24	20	20	40	20	50
Lateral reticular cells (respiratory)		50	16	24	12	80	22	30	0	5

TABLE 3A

PERCENTAGE OF CELL DAMAGE IN HYPOTHALAMUS IN CASES WITH PULMONARY EDEMA

Case No.	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.
Supraoptic	10	15	15	22	17	15	15	20	15	22
Paraventricular	15	12	8	5	0	6	5	15	5	13
Tuberal	0	8	5	0	0	5	5	5	0	12
Medial	10	6	6	0	5	5	17	10	12	16
Lateral	0	5	5	10	5	0	15	15	5	16
Posterior	10	6	5	0	12	0	0	10	0	0
Mamillary	0	0	0	0	5	5	0	0	0	5

light-staining cell, which was identified chiefly by the still intact nucleus. Later, even the nucleus underwent changes, becoming eccentrically placed, losing its staining properties, and eventually showing fragmentation, pyknosis, and extrusion from the cell. All the above changes are readily determined in the larger cells such as the supraoptic and the paraventricular nucleus. However, great caution had to be exerted in a study of cell changes occurring in the smaller cells comprising the remaining cell groups. Mild changes such as dissolution of Nissl substance and eccentricity of nuclei could not be relied on as definite evidence of cell injury. Only more extreme changes were accepted such as cellular swelling, formation of ghost cells, pyknosis of the cell or its nucleus, fragmentation of the cell or its processes, or neuronophagia. Using these criteria, the changes observed in each of the ten cases with pulmonary edema are tabulated in table 3A and the alterations observed in the five control cases without lung changes in table 3B.

A comparison of involvement of the hypothalamic nuclei in patients with and without pulmonary edema revealed no definite differences between the two groups (tables 3A and 3B). From a study of these nuclear changes, one could find no indication that damage to these nuclei played any role in the production of pulmonary changes.

Cerebral Hemispheres

Within the cerebral hemispheres, sections were removed and studied from the following areas: hippocampus, corpus cinguli, corpus callosum, inferior frontal gyrus, prefrontal area, superior parietal gyrus, inferior parietal gyrus, superior temporal gyrus, transverse temporal gyrus, inferior temporal gyrus, lateral occipital gyrus, and the calcerine gyrus. Clearcut and consistent changes were observed in all cases and consisted of both inflammatory and neuronal alterations. The inflammatory changes were mild and observed chiefly in the superior precentral area. Neuronal damage was much more striking but was limited to the large and medium pyramidal cells of the motor cortex.

TABLE 3B

PERCENTAGE OF CELL DAMAGE IN HYPOTHALAMUS IN CASES WITHOUT PULMONARY EDEMA

Case No.	11.	12.	13.	14.	15.
Supraoptic	15	25	20	17	15
Paraventricular	10	0	15	5	6
Tuberal	0	0	8	6	0
Medial	0	0	0	7	18
Lateral	15	0	10	5	12
Posterior	5	0	6	0	6
Mamillary	5	0	0	5	0

There was no difference in the degree or extent of the changes within the cerebral hemispheres in those cases with or without pulmonary edema. None of these cases showed any pathologic evidence of cerebral edema and none had clinical evidence of increased intracranial pressure.

DISCUSSION

In spite of extensive experimental work, there is at present no accepted etiology for the so-called neurogenic pulmonary edema. Many theories have been proposed based primarily on the production of the edema by various experimental methods. In view of the pulmonary changes resulting from vagotomy, it has been suggested that the vagi offer strong parasympathetic vasoconstrictor fibers to the pulmonary vessels. Vagus involvement, therefore, either peripherally, as in vagotomy, or centrally, as in medullary damage, produces a loss of bronchomotor tone and deprives the pulmonary vessels of mechanisms necessary in the adjustment of pulmonary vascular dynamics.[11,19] In addition, tachycardia results, with failure of the heart to adjust to circulatory changes and hence a mechanical rise in filtration pressure in the alveolar capillaries. This latter in the presence of poor bronchomotor tone, hence an absence of a compensatory rise in intraalveolar pressure, results in the edema. Although it is known that the blood vessels in the lungs are supplied with both parasympathetic and sympathetic nerve fibers,[30,31] the actual problem of regulatory mechanism for the pulmonary vascular bed is still unsettled, and there is considerable doubt

about the importance of this regulatory mechanism to the problem of pulmonary edema. Moreover, most of the evidence at the present time would seem to indicate that bilateral vagal destruction alone will not result in pulmonary edema as long as the airway is kept open.

Sarnoff and Sarnoff,[20] from their experiments on dogs, felt that medullary involvement may cause a stimulation of the cardiovascular centers, with a resulting elevation of pulmonary and systemic arterial and venous pressures causing edema. They believed that the term "neurogenic" should be replaced by the term "neurohemodynamic pulmonary edema," since the edema results from an increase in the rate of transfer of fluid from pulmonary capillary to the extravascular space of the lung by an increase in pulmonary capillary pressure, which in turn is brought about either directly or indirectly by nerve impulses.

From our own studies, it is apparent that two distinct neurologic lesions are always necessary to result in pulmonary edema. These consist of destruction of 1) the dorsal nucleus of the vagus, and 2) the vasomotor centers within the brainstem. Damage to only one of these centers does not result in pulmonary changes. Involvement of the vagal centers may well produce a loss of bronchovascular tone, with an associated inability of these vessels to adjust to changes in pulmonary vascular dynamics, and this loss may be an important factor in the subsequent development of pulmonary edema. However, it is our feeling that, in addition to the above possible factor, tachycardia in the presence of a damaged vasomotor center results in rapid onset of heart failure. This heart failure with its resulting increased pulmonary venous and capillary pressure probably is the single most important factor in the production of pulmonary edema. For this reason, involvement of the vasomotor centers in the medulla becomes a very essential factor in the production of pulmonary changes. A brief outline of our concept of the etiology of pulmonary edema based on our pathologic findings is tabulated in table 4.

The role played by the cerebral hemispheres in the production of cerebral edema was not clarified by our studies. Certainly changes in the motor cortex do not seem to influence pulmonary physiology. The part that other brain areas might play in this process could not be determined from our studies, since in bulbar poliomyelitis most areas of the

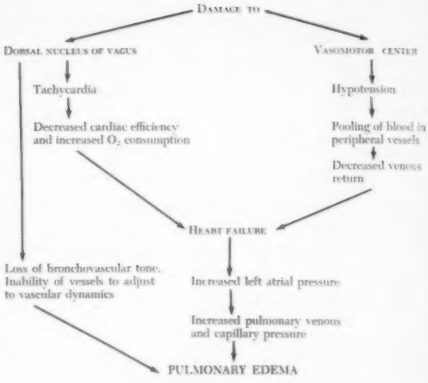
Damage to
Dorsal nucleus of vagus
Vasomotor center
Tachycardia
Hypotension
Decreased cardiac efficiency and increased O_2 consumption
Pooling of blood in peripheral vessels
Decreased venous return
Heart failure
Loss of bronchovascular tone. Inability of vessels to adjust to vascular dynamics
Increased left atrial pressure
Increased pulmonary venous and capillary pressure
Pulmonary edema

Table 4.

cerebral hemispheres are not involved. Most of the experimental studies implicating the brain in pulmonary edema depend upon the production of increased intracranial pressure, and it might be suggested that the resulting pulmonary changes may be due to the referred effects of the increased pressure upon the medullary centers rather than upon the cerebral hemispheres themselves.

CONCLUSIONS

1. A detailed histopathologic study was made of the nervous system of ten fatal cases of bulbar poliomyelitis with extensive pulmonary edema and five cases without lung changes, in an attempt to determine whether specific neurologic lesions might be responsible for the pulmonary edema.

2. All cases with pulmonary edema revealed extensive damage to both the dorsal nuclei of the vagus and to the medial reticular nuclei (vasomotor) of the medulla. Pulmonary edema did not result from involvement of only one of the above cell groups. The control cases without pulmonary edema did not reveal this same consistency of damage to these two nuclear groups.

3. It was felt that the most important factor in the production of this neurogenic type of pulmonary edema was the resulting heart failure produced by 1) tachycardia and decreased cardiac efficiency due to vagal damage, and 2) vasomotor collapse secondary to involvement of the vasomotor center. This resulting heart failure produces increased left atrial pressure, with a subsequent increased pulmonary venous and capillary pressure and finally edema.

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■ Vesalius was the most celebrated anatomist of his time. He took great pains in endeavouring to detect and expose the errors, and to detract from the reputation, of Galen, to whom the medical world had looked up for many centuries. He not only calls in question the anatomical knowledge of Galen, but states his firm belief that that celebrated person had never dissected the human subject, but had obtained what knowledge he possessed by the examination of the bodies of apes and other brute animals.

John Cooke in *A Treatise on Nervous Diseases*, published in 1824.

Reading Epilepsy

A. Bingel, M.D.

SEIZURES are rarely produced by exogenous factors alone. In cases of so-called musicogenic epilepsy, a sound, music, or sometimes only a certain melody may precipitate an epileptic attack. Critchley[1] in 1937 reviewed the literature of such cases and added 11 interesting ones from his own observations. Other patients have attacks solely upon activation with light, either bright light or flicker light. The precipitation of organic convulsive attacks by reading will be emphasized in this communication. Bickford[2] mentioned such a possibility and referred to investigations in which patients reported that prolonged reading gave rise to an attack, usually consisting of generalized convulsions preceded by an aura of "clicking" or movement of the jaw. Our own observations of epileptic seizures provoked by reading consist of three cases offering a number of interesting problems.

Case 1. On May 9, 1950 a 21 year old soldier was admitted to a U. S. Army Station Hospital in Georgia. There was a history of grand mal seizures for the previous year and a half. All seizures occurred while he was reading. The patient described the sequence of events as follows: "While reading I suddenly come to a certain point where I begin to stutter and am not able to read any further; shortly thereafter I lose consciousness and have a seizure involving both arms and legs." Such a seizure usually lasted for five to ten minutes and was followed by lethargy and confusion. No fecal or urinary incontinence was ever noticed and the patient did not injure himself or bite his tongue. There was no history of injury to the head or the vertebral column. Physical and neurologic examinations during this first hospitalization did not reveal any abnormalities. After a short observation, the patient was transferred to Walter Reed Army Hospital in Washington, D.C. where the physical examination was again normal, as were routine blood studies, fasting blood sugar, urinalysis, and chest and skull roentgenograms. The routine electroencephalogram was normal; however, under Metrazol activation an abnormal electroencephalogram showed a petit mal type pattern, most pronounced in both frontal and parietal areas. After injection of 425 mg. of Metrazol the patient had a grand mal seizure. Since the seizures were apparently well controlled on Dilantin and phenobarbital, he was returned to duty with a diagnosis of epilepsy, grand mal, mild, cause undetermined.

In August 1950 the patient was admitted to the neurology service of Brooke Army Hospital for evaluation. He wanted to re-enlist, but could not be accepted with a diagnosis of epilepsy. He gave the same history as before, adding that he had the first seizure one night while lying in his bed reading for 30 to 45 minutes. He related that he suddenly came to a word where he had to stop reading, because he could not get over the word, even though it was not a difficult one. He stuttered or stammered and this recurred several times until he suddenly lost consciousness and went into a seizure. In this episode, and also in several later instances, he read aloud; on several other occasions he also provoked a seizure by silent reading.

The patient was a well developed white male. He was oriented, alert, and cooperative. Both physical and neurologic examinations did not reveal any significant abnormalities. Laboratory examinations showed negative blood and urine studies. Roentgen examinations of chest and skull were normal. A spinal puncture revealed normal pressure, clear fluid with no cells, 68 mg. sugar per ml., 690 mg. chlorides per ml., 76.5 mg. per ml. total protein, a flat gold curve, and a negative complement fixation reaction in all dilutions. A repeated spinal fluid examination about one month later showed 76.5 mg. per ml. total protein and otherwise normal results. An awake electroencephalogram on August 16, 1950 revealed a mildly disorganized and irregular tracing, with a dominant rhythm of 10 to 11 per second medium voltage activity in all leads. There were no true focal or paroxysmal signs and hyperventilation produced only a slight build-up. The sleep record, however, was interpreted as abnormal, suggestive of a convulsive disorder, grand mal type, without focal signs.

During the course in the hospital the patient was seen on many occasions for further neurologic evaluation and these examinations were consistently negative. The only persistent abnormal laboratory findings were an elevated spinal fluid protein and an abnormal electroencephalographic sleep record. On November 10, 1950 it was decided that a "reading trial" should be made. The patient was given an article from a current magazine, which he began to read loudly and fluently while sitting in a comfortable chair. After two minutes of reading, slight hesitation and stammering were noticed. After three minutes the patient again stammered for a few seconds but then continued reading. This was repeated after five and six minutes of reading. Seven minutes after the beginning of reading he suddenly dropped his book, leaned backward in the chair, and stretched out both legs. The facial color became pale; then tonic contractions in both arms and legs appeared

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simultaneously, with complete loss of consciousness. After five seconds the tonic phase was followed by clonic movements involving the facial muscles and the arms and legs equally. The color of the face became progressively more cyanotic. After about three minutes the clonic phase ended and was followed by a period of deep sleep with stertorous breathing. During this period the extremities were flaccid. During the seizure pupillary reactions to light were diminished; a Babinski sign could not be elicited. After about ten minutes the patient began to show the first reactions to external stimuli.

On November 20, 1950 the reading test was repeated; a tape recording of the reading and a moving picture of the ensuing grand mal seizure were made. On this date, however, it took 45 minutes of reading before a grand mal attack was precipitated. The patient again expressed his willingness to cooperate in a third reading test which was done in the electroencephalographic laboratory. He read for about 50 minutes without stammering or stuttering, no abnormal recordings could be obtained, and there was no seizure. On his way back to the ward, the patient stated that during this last test he became afraid of having another seizure and that he tried very hard to avoid the attack. He already knew how to do that, namely by reading absolutely mechanically and without any inner participation in the content of the material read. No other attempt at provocation was made thereafter.

A pneumoencephalogram was done on November 28, 1950. It showed normal air-filling of the entire ventricular system and the subarachnoid spaces, with no evidence of abnormal defect or displacement. Psychologic testing on November 14, 1950, including administration of Wechsler-Bellevue test, Bender Motor Gestalt test, Minnesota multiphasic test, sentence completion test, Rorschach method, and Goldstein-Scheerer test, indicated that basically the patient was of average intelligence, with some further indication of mild organic impairment. Thought processes functioned at a concrete level, with marked emphasis on details and disregard of more abstract or general concepts. The mode of thinking showed no capacity of originality. Emotionally, the records showed definite flatness or dullness with constriction of behavior. While there was slight evidence of immaturity and impulsivity, there was also evidence of strong repressive control. No evidence of warm relationship with other human beings was found. In addition, there were minor but consistent indications of borderline organicity: perseveration, perplexity, and unsureness. A sodium Amytal interview revealed that the patient did not have any recollection of the events during a seizure.

An attempt was made to provoke an epileptic seizure by prolonged writing to dictation, but this attempt was unsuccessful. It should be mentioned that an attack could never be induced by speaking or any activity other than reading.

The patient was discharged from the hospital after having met a physical evaluation board which considered him unfit for military duty. He was placed on anticonvulsant medication with Dilantin 100 mg. and phenobarbital 32 mg. each three times daily. It was not possible to examine the patient again, but frequent contacts were made by mail. In July 1953, for instance, the patient reported that he had discontinued phenobarbital and Dilantin treatment, since taking the medication for more than one year did not seem to be of any benefit. At that time he had restricted his reading and thus did not have a seizure for about one year. He worked steadily in a mill. In July 1955 he reported that for a time he had tried to read but had recurrent seizures and therefore had to again restrict reading to a minimum. He continued working regularly and did not have any other complaints.

Case 2. A 19 year old soldier reported that he had his first seizure in September 1955 while riding on a bus and reading a novel. It was around noon when he lost consciousness and afterward his tongue felt sore. The second attack occurred one night in January 1956, shortly after midnight while he was lying on his bed reading. He had a sudden sensation that everything would stop and at the same time he felt as if he would swallow his tongue. He thinks that he subsequently had a grand mal seizure, associated with tongue biting, but without loss of bladder control. One night in March 1956, while he was again reading, the third attack occurred. He had a vague forewarning and stopped reading. He soon felt better and continued reading, but after a few minutes went into a grand mal seizure in which he fell out of bed and bit his tongue. During the latter part of May 1956, while stationed in Iceland, he had a fourth seizure while lying in his bed reading. He again had a certain forewarning, a sensation that he would swallow his tongue; then he had a grand mal seizure which was observed and described by a medical officer.

All these seizures occurred while the patient was reading and only after prolonged reading of one to two hours. Reading was not always followed by an epileptic attack and at times he could read all afternoon without having any forewarning symptoms and without experiencing a seizure. At other times he read only for a few minutes, then had a forewarning which caused him to stop reading; thus, he was able to avoid the attack. There was no specific type of literature that precipitated a seizure. After a seizure he did not read for several days for fear he might thereby produce another one. Watching a moving picture or television did not provoke a seizure, nor did writing, talking, or listening to music. In all seizure occurrences the patient remembered a marked loss of sleep the preceding night. To avoid seizures the patient as a general rule did not read longer than 30 to 45 minutes and he especially avoided reading at night in his bed.

Asked again about the forewarning symptoms, the patient stated that it could be a sensation like a hammering of the heart, a twitching or quivering of the tongue with a feeling as if the tongue would go up to the roof of the mouth. Thereafter his vision was often blurred for one or two seconds and everything stopped—thinking and reading. Before the seizure he often tried to say a word but was unable to do so and then he had a convulsion. After an attack he felt sleepy and sore in all his joints. In January 1956 he took "capsules" for a few days. Whenever he felt that he might have an attack he took a phenobarbital tablet.

The patient was admitted to the neurology ward of Brooke Army Hospital in July 1956. The physical examination, including a thorough neurologic evaluation, did not reveal any significant findings. Chest and skull roentgenograms were negative. A spinal puncture revealed normal pressure, clear fluid with normal cell count, normal total protein, a normal gold curve, and a negative cardiolipin test. An arteriogram showed a normal internal carotid vascular system bilaterally; a pneumoencephalogram revealed a slight dilatation of the ventricular system which was more pronounced on the left.

The first electroencephalogram showed several bursts of three per second spike-and-dome complexes in all left leads during drowsiness. A single burst of six per second positive spikes appeared on the right. Some spike-like activity also occurred in both temporal leads. A second electroencephalogram showed an amplitude asymmetry between the left and right occipital leads, the high voltage waves being more prominent on the right. Photic stimulation did not produce photic driving. During reading aloud a disappearance of alpha rhythm with replacement by muscle potentials was noted.

Case 3. A 23 year old sergeant, seen in the neurology clinic of Brooke Army Hospital in August 1953, gave a history of six previous grand mal seizures since the fall of 1949. Two of these seizures occurred after prolonged reading and four after playing cards for several hours. The patient reported that he could read or play cards for one or two hours without any difficulty, but continuing for a longer period of time provoked a sensation of spots before his eyes, blurred vision, and a feeling that he would "pass out." In each of these six instances, he had actually lost consciousness and had a seizure. According to the patient's description, the seizures seemed to be typical grand mal attacks without focal features. In one of these attacks he bit his tongue and lost bladder control. The patient thought that the prolonged and increased mental concentration caused his seizures. In both instances he read "true" or "adventure" stories when he had a seizure. He had had between two and four bottles of beer in two of four instances when a seizure was precipitated by prolonged playing of cards. In all cases he had smoked a number of cigarettes prior to the seizure.

The general physical and neurologic examinations of this well developed man were normal. Roentgenologic findings of chest and skull were normal. It was not possible to do a spinal puncture. The electroencephalogram was normal while awake, but during sleep the record was abnormal, with one burst of six per second positive spikes in the right temporal area and one petit mal type burst in both frontal and parietal areas. The patient was placed on Dilantin medication, 100 mg. three times a day, and two 32 mg. tablets of phenobarbital at bedtime. He was seen for a few follow-up visits at monthly intervals. It soon became apparent that he did not take his medicine regularly, because he felt very well and did not have any attacks as long as he avoided prolonged card playing and reading.

DISCUSSION

There seems to be no doubt that seizures were precipitated by reading in all three cases. In the seizures no focal signs were seen. No evidence of focal origin was elicited in the neurologic examinations or electroencephalograms.

There may be two distinct types of reading precipitation, namely a precipitation after a short period of reading as in most episodes of case 1, or after prolonged reading as in cases 2 and 3. Whether there are quantitative differences in intensity of the provocative stimulus or additional irritating factors, such as fatigue, will be discussed later.

It is interesting to consider the possibilities of the underlying mechanism of precipitation in these cases. Bickford[2] suggested a visual stimulus and this certainly is a good possibility, considering the fact that during reading the eyes perform saccadic lateral movements with fixational pauses.[3,4] During quick lateral eye movements no visual perception is possible, and this interrupted visual stimulus during reading may be similar to photic stimulation. We know, furthermore, that reading with increased attention may produce a higher number of fixational pauses or perhaps a stronger cortical irritation.[5] This factor seems to be of special interest in that the first patient more readily had a seizure whenever he read with greater attention on the basis of a higher, now critical and driving photic frequency. Perhaps in our first case the pre-ictal arrests of reading were a stop of the saccadic eye movement, caused by an increased duration of a fixational pause in which no further reading was possible. The patient himself once stated that his eyes stopped at one word and he could not see the following words.

It should be remembered that disturbances of reading can be part of an aphasic symp-

tomatology and, therefore, reading epilepsy might belong to the group of so-called aphasic seizures. The similarity of our first observation with the case *A.R.* described by Penfield and Jasper[6] is rather apparent. Their patient showed a "sudden inability to understand the printed word and an inability to find words he needed to express his meaning. While reading he might suddenly fail to understand in the midst of a sentence. He habitually tried to re-read the sentence several times and then it would occur to him that this was an attack and he would sit back to wait for the condition to pass off." The difference, however, between this and our observations is also obvious. In the case of *A.R.* aphasia was the only manifestation of the epileptic attack, and in our cases the reading difficulty was a true prodroma and not a part of the subsequent generalized convulsive seizure. It seems unlikely that there is a specific relationship between these three cases and aphasic seizures. Speaking never produced an attack in our three cases. It should also be mentioned that Gordon[7] in 1928 published an observation of precipitation of a grand mal seizure by writing. While writing to dictation, this patient continued making errors before he fell off his chair and convulsed. It was not possible to duplicate this kind of precipitation and the patient had more seizures without writing. In our cases writing had no activating influence.

Reading could be a rather specific stimulus which would be able to precipitate a severe irritative response from a functionally related cerebral structure or focus. We are reminded that optic, acoustic, olfactory, or gustatory stimuli in animal experiments can provoke a seizure-like attack if there are lesions in corresponding cerebral centers.[8] A sensitive cortical area, due to an organic lesion, can be induced by a specific stimulus to produce a strong irritative response which, by centrencephalic stimulation, may initiate a general seizure discharge. A cerebral reading center, however, is still hypothetical, and the clinical correlation of these three cases did not reveal signs of a focal cerebral lesion. It should be kept in mind that the possibility of a slowly growing intracranial mass cannot be completely excluded in these cases, even though pneumoencephalograms, arteriograms, and electroencephalograms were done. In the first case an elevated cerebrospinal fluid protein was noted, but further observation extended over a period of more than five years.

If an underlying organic localized cerebral lesion cannot be revealed in our cases, it must be assumed that there is at least some alteration of the activity of the cerebral neurons which is the basis of the epileptic predisposition. In such a case it may be presumed that reading is a specific trigger mechanism which sets off an epileptic seizure. A final decision about the method of this precipitation, whether optic or aphasic or through a cerebral reading center, is not possible at this time. A disturbance within the optic pathways, however, seems to play an important role.

There are a few more interesting signs or symptoms to be mentioned from these observations. This is a special group of epileptic patients who are not only reacting to a specific stimulus alone, but who are also asymptomatic as soon as this stimulus is avoided. For this reason it is postulated that these cases should be grouped in a special category of epilepsies which would include many cases of musicogenic epilepsy, a certain number of photogenic epilepsies, and perhaps even writing epilepsies. We would call them "exogenously precipitated epilepsies," and add that, after a number of primary experiences, the patient will soon learn to avoid the overt manifestation of his epilepsy. In addition, it is interesting to note that the first case was able to suppress an epileptic seizure by reading without attention or inner participation in the content of the material read. This suppression of attacks by mechanical reading points to involvement of the highest level of neuronal integration. Critchley's case 3 had a very similar experience; he would hear music without listening to it and no attack would follow.

Finally, it may be stressed that two groups of reading epilepsies can be distinguished: one with a short latency of five to ten minutes, the other with a longer latency of more than 30 to 40 minutes. The former type is rare; we saw only one case in five years among a large number of young epileptics. In the latter group it is apparent that fatigue plays an important role in facilitating the brain for the specific stimulus and thereby lowers the convulsive threshold.

The prognosis of these conditions is not sufficiently known; since seizures can be avoided, one would think that the over-all prognosis is good. In this connection, it might be worthwhile to recall that one of Critchley's patients with musicogenic epilepsy (case 7) lost his susceptibility toward music and finally was able to attend concerts during the last ten years of his life.

SUMMARY

Three cases are described in which organic convulsive attacks of grand mal type were precipitated by reading. In one case the period of reading was rather short and in two other cases epileptic attacks were provoked after prolonged reading. In these latter observations an additional factor, namely fatigue, probably played an important role. Reading epilepsy apparently belongs to a special group of epilepsies which depend on a specific precipitating factor, similar to musicogenic epilepsy, certain cases of photogenic epilepsy, and perhaps writing epilepsy. It is suggested that this group should be called exogenously precipitated epilepsies.

The characteristic features of this group are as follows:

1. An underlying susceptibility to seizures without true focal signs must be assumed (predisposition).

2. Precipitation by a specific factor, such as reading; in other cases by music, light, writing, even by smelling and tasting.

3. Cases of reading epilepsy with longer latency are preceded by lack of sleep and by fatigue.

4. By actively decreasing attention or participation toward or in the content of the precipitating factor, a possibility of suppressing such seizures exists.

5. Anticonvulsant medication is usually ineffective.

The possibilities of the mechanism of precipitation are discussed. It is thought that a lesion within the optic pathways could be an important pathogenic factor in reading epilepsy.

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■ Dr. Cullen considers epilepsy as a genus of the order, spasmi, and divides it into the *idiopathic* and *symptomatic;* the first including three species, the *cerebralis,* the *sympathica,* and the *occasionalis;* the second containing a great number of species, according to the various diseases with which it may be connected, or by which it may have been caused.

The first species of idiopathic epilepsy, the *cerebralis,* arises suddenly, without any mainfest cause, and is not preceded by any troublesome sensation, except perhaps vertigo or scotomia; the second, the *sympathica,* also arises without any manifest cause, but it is preceded by the sensation called the aura epileptica, proceeding from some part of the body, and ascending towards the head; and the third, the *occasionalis,* is produced by some evident irritation, and ceases on the removal of that irritation. The symptomatic epilepsies, as above mentioned, receive their names from the diseases to which they are related.

John Cooke in *A Treatise on Nervous Diseases,* published in 1824.

Observations Upon Responses to Digital Carotid Artery Compression

In Hemiplegic or Hemiparetic Patients

J. E. Webster, M.D. and F. S. Gurdjian, M.D.

DURING THE PAST YEAR digital carotid compression tests have been added to our routine measures employed in a neurologic examination. This maneuver is carried out with the patient in a sitting position, either upon a bed or examining table. Standing at the side of the patient for compression, the examiner then uses his second, third and fourth fingers to compress the carotid bulb against the spine to produce gradually a total occlusion. Compression is continued depending upon the patient's response. The right and then the left carotid is compressed. The pulse is recorded by an assistant during the period of compression. It is essential in the test that the carotid bulb be compressed and that occlusion of both the external and internal carotid arteries be complete. One hundred patients with hemiplegia or paresis due to various causes were tested by digital carotid bulb compression and the responses analyzed for this report. Simultaneous electroencephalograms and electrocardiographs were made upon many patients, as well as movies for analysis of the responses.

TYPES OF RESPONSES TO DIGITAL CAROTID BULB COMPRESSION

The responses to digital carotid compression were correlated with the individual neurologic, angiographic, pneumoencephalographic studies, and operation or autopsy.

The responses in summary were:

1. Temporary unilateral digital carotid compression in normal patients had no effect except for discomfort from the neck pressure.

Syncopal Responses

2. Occasionally compression resulted in an abrupt cardiac asystole due to stimulating a "sensitive carotid sinus." The patient immediately lost consciousness and simultaneous clonic convulsive movements occurred. The cardiac responses can usually be abolished by intravenous administration of atropine sulfate gr. 1/100.

3. Contralateral carotid compression resulted in syncope in patients with partial or complete occlusion of the carotid artery of recent origin. This syncope is quite similar to that associated with the cardiac asystole induced by a neural mechanism, termed previously the "cerebral type" of irritable carotid sinus response. After compression is applied, the susceptible patient usually develops an increased respiratory rate, pallor, dizziness, blurring of vision with convulsive movements, and then syncope. Recovery to normal is rapid upon releasing the compression and placing the patient in a recumbent position. In patients with carotid occlusions, however, there is usually neither a major fall in the peripheral blood pressure nor prolonged asystole of the heart, although cardiac slowing often occurs. There is a pronounced fall in the cerebral blood pressure (figure 1).

4. In some patients both a "sensitivity" of the carotid sinus and a carotid insufficiency may co-exist with syncope occurring as in 2. When atropine gr. 1/100 is administered intravenously, syncope still occurs but without heart block as in 3.

5. In patients with basilar artery occlusion with hemiplegia or hemiparesis, syncope was produced by compression of either the right or left carotid artery.

6. In patients with both right and left carotid insufficiency, compression of either carotid also resulted in syncope, thus producing the same type of response as in 5.

7. Patients having an occlusion of the anterior cerebral artery, with or without a hemiplegia or hemiparesis, usually develop syncope when the contralateral carotid is occluded.

Non-syncopal Responses

8. Hemiplegic or paretic patients did not respond by syncope when the middle cerebral trunk artery was occluded. The paralysis was usually of a severe degree in these patients.

9. There was found to be a group of patients with recent (and chronic) hemiplegia having normal angiographic studies who did not develop syncope upon carotid compression (similar to the patient with an occlusion of the middle cerebral trunk artery).

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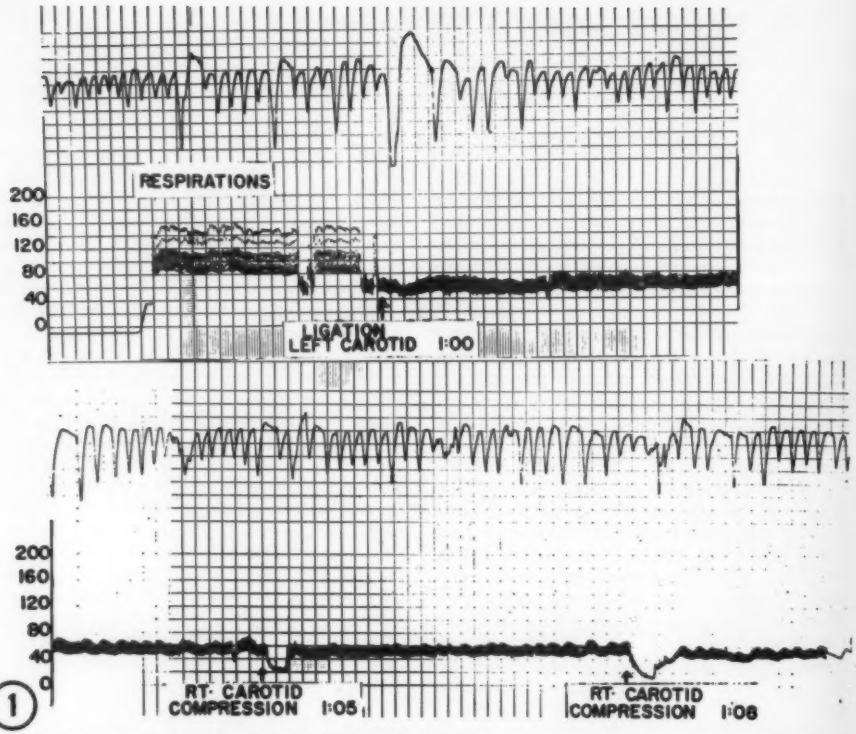

FIG. 1. Continuous blood pressure recorded from the carotid artery in a patient having an acute ligation of one carotid artery (for aneurism). Note fall in pressure to 50 mm. after ligation. When the contralateral carotid artery was occluded by digital compression, the intracarotid pressure fell to 10 mm. and the patient developed syncope. (After 7 days this patient then developed tolerance to contralateral compression even in the upright position.) Normal brachial pressure (Cuff) 140/80.

10. In patients with hemiplegia or hemiparesis due to a brain tumor or mass lesion, degenerative, inflammatory disease, or trauma, syncope usually did not occur upon contralateral carotid compression.

SAFETY

Care is taken during digital compression of the carotid to stop the occlusion at the earliest sign of syncope or of convulsive movements. The symptoms of increased respirations, dizziness, faintness, blurring of vision, and twitching movements warn that syncope may follow. At the first sign of loss of consciousness the patient is placed in the supine position. Usually, compression for 10 to 20 seconds is required before syncope occurs from the induced acute cerebral vascular ischemia. An immediate onset of syncope (5 seconds) usually indicates a "sensitive carotid sinus," which is much less common than the delayed type of syncopal response due to a vascular occlusion (10 to 30 seconds).

Within our experience, one patient developed an increased degree of paralysis 12 hours after compression tests were made; another had electrocardiographic evidence of increased coronary damage. No other serious complications have been encountered. Caution, however, is used in performing the tests.

CORRELATION OF TESTS IN PATIENTS WITH HEMIPLEGIA AND HEMIPARESIS

In general, the response to digital carotid compression was found to vary depending upon the cause for the hemiplegia or hemiparesis. Syncope nearly always occurred when recent occlusive disease of the carotid, basilar,

FIG. 2 and 3. Example of angiographic patterns in patients with complete (2) or partial (3) carotid artery occlusion. Contralateral digital carotid compression may produce syncope with convulsive movements in the recent hemiparetic or hemiplegic patient caused by these lesions.

FIG. 4 and 5. Example of anterior cerebral artery occlusion. Contralateral digital carotid artery compression usually results in syncope. (Hemiplegia or hemiparesis may not be present although it was in the patients in this analysis.)

or anterior cerebral artery was responsible for the neurologic state, but not when the middle cerebral artery or its branches were involved. Syncope did not occur in patients whose neurologic deficits were due to inflammatory or degenerative diseases, trauma, or a mass lesion, unless an associated cerebrovascular insufficiency or "sensitive carotid sinus" was present. The promptness of development of the loss of consciousness in patients with cerebrovascular occlusions depended upon the degree of collateral flow which had been or could be established (figures 2 and 3).

Elderly patients with generalized atherosclerosis who sometimes responded to compression by syncope still harbored a mass lesion. This was found in six instances. The existence of increased intracranial pressure suggests a pathophysiologic basis for syncope. In these patients either ipsilateral or contralateral carotid compression may reduce the intravascular pressure to a degree that the extravascular pressure due to the tumor produces major arterial occlusions, thus diminishing blood flow to brainstem centers.

A "sensitive carotid sinus" may complicate interpretation of the response to carotid compression. When suspected, a simultaneous electrocardiogram before and after atropinization may be helpful. Atropine may prevent the cardiac asystole and thus the syncope from the sinus stimulation. If the syncope still occurs following atropinization without asystole, then occlusive disease is probable.

The observation has been made frequently that the patient with a unilateral anterior cerebral artery occlusion (both with and without paralysis) may develop syncope upon compression of the contralateral carotid bulb. Since the distal portion of the occluded vessel often filled by angiographic injection from the opposite side, this was earlier thought to be an artifact or technical abnormality (figures 4 and 5).

Syncope was found to occur upon both right and left carotid compression in patients with occlusion involving the basilar artery. Quadriplegic or paretic signs were usually present with ophthalmologic disturbances among those patients with basilar artery involvement. Only a few patients in this class, however, have been tested (figures 6 and 7).

When the hemiplegia or hemiparesis was due to an occlusion of the middle cerebral artery trunk, with few exceptions, syncope did not occur. An exception was one patient having, in addition, an anterior cerebral artery occlusion on the opposite side. Also, syncope did not occur in some patients with recent and chronic hemiplegia who presented "normal" angiograms of the major cerebral vessels and the carotids. The possibility of embolic phenomena with dissolution of the embolus or generalized small artery involvement by arteriosclerosis may explain the findings in this group (figures 8 and 9).

It has been noted that the reaction to the first compression test is maximal. Thereafter, moderation of the response occurs until syncope may not develop as the circulation is conditioned by the compression. In carotid artery thrombosis, tolerance to contralateral compression may develop over a period of several months. There were three examples of no syncopal responses in chronic carotid occlusions. Patients having had a ligation of the carotid artery for an aneurysm may not immediately tolerate contralateral carotid compression but do so after a week to several months (figure 10).

ANALYSIS OF 100 CASES

RESPONSE TO DIGITAL CAROTID COMPRESSION

I. *Syncopal Responses*

A. Carotid Occlusion (cases 29)
(with hemiplegia-hemiparesis)

1. Complete unilateral occlusion (case 17)

syncope	no syncope
13	4—1 with bilateral occlusion but with good collaterals

2. Incomplete unilateral occlusion (case 12)
(insufficiency syndrome)

syncope	no syncope
11	1

Comment: Two patients not responding by syncope in group I were longstanding cases (7 months, 1½ years) as was the one patient in group II.

B. Basilar Occlusion (cases 7)
(with hemiplegia-hemiparesis)

syncope	no syncope
6	1

Comment: The syncopal response in this group occurred either upon right or left compression. This response was similar to two patients with bilateral incomplete carotid occlusions. The exception was a patient with partial occlusion of 2 years duration.

C. Anterior Cerebral Artery Occlusion (cases 10)
(usually hemiparesis greatest in upper extremity)

syncope	no syncope
9	1

Comment: Patients having this lesion without pa-

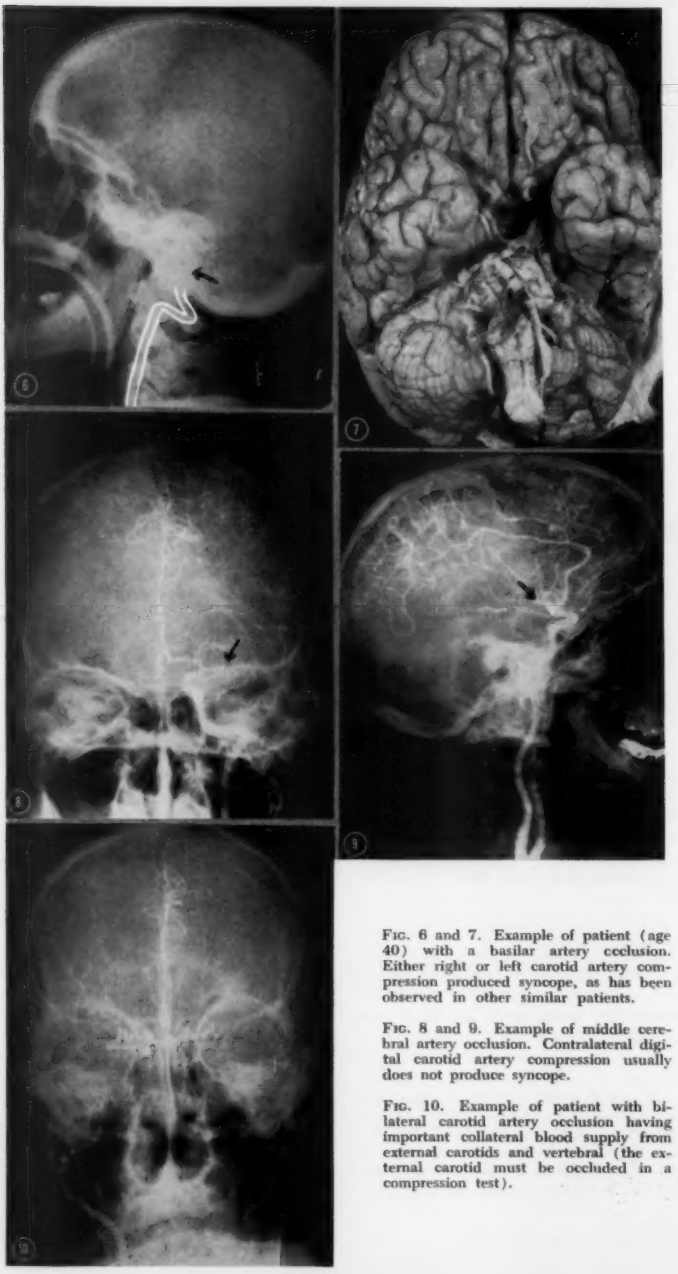

FIG. 6 and 7. Example of patient (age 40) with a basilar artery occlusion. Either right or left carotid artery compression produced syncope, as has been observed in other similar patients.

FIG. 8 and 9. Example of middle cerebral artery occlusion. Contralateral digital carotid artery compression usually does not produce syncope.

FIG. 10. Example of patient with bilateral carotid artery occlusion having important collateral blood supply from external carotids and vertebral (the external carotid must be occluded in a compression test).

ralysis also were found to develop syncope when the contralateral anterior cerebral was temporarily occluded by carotid compression.

II. *Non-syncopal Responses*

D. Middle Cerebral Artery Occlusion (cases 10)

syncope	no syncope
3	7

Comment: One of the patients in the syncopal group also had an occlusion of the anterior cerebral artery. One in the non-syncopal group had a chronic carotid occlusion with an acute middle cerebral artery trunk occlusion.

E. Small Artery Arteriosclerosis or Emboli with Ischemia or Infarction (cases 10) (normal angiogram)

syncope	no syncope
0	10

F. Mass Lesions (brain tumor, hematoma) (cases 26) (with hemiplegia-hemiparesis)

syncope	no syncope
6	20

Comment: Of the patients responding by syncope one presented a sensitive carotid sinus; one was 70 years of age; two had papilledema (one patient with a chronic subdural hematoma also responded by syncope).

G. Encephalitis-Meningitis-Multiple Sclerosis-Trauma (cases 8) (with hemiparesis)

syncope	no syncope
0	8

Comment: Two of these patients were children.

Note: In patients where syncope was expected (46) there were exceptions or misleading responses in 7 or 15%.

In patients where syncope was not expected (54) there were exceptions or misleading responses in 9 or 16%.

The factors influencing the response include length or time of occlusion (collateral circulation), the presence of a sensitive carotid sinus, increased intracranial pressure or a partial carotid occlusion accompanying other lesions. Evaluation of these factors increases the accuracy in evaluating the compression test.

SUMMARY

Temporary digital carotid artery compression is a valuable and safe neurologic test for identifying occlusive cerebral vascular disease, particularly when hemiplegia or hemiparesis is recently present or developing.

This carotid compression test has now been cautiously employed in several hundred patients in all age groups with but few complications.

When syncope is induced by temporary digital carotid compression on the side of the paralysis or paresis, contralateral carotid occlusive disease is probable. This response is not accompanied by a heart block, characteristic of the carotid sinus reflex, although heart slowing may occur. When syncope does not occur, there is a likelihood of a nonvascular type of neurologic lesion caused by a brain tumor, inflammatory or degenerative disease, or trauma. If syncope occurs upon compression at the right and left carotid bulbs, then occlusive disease of the basilar artery, complete or partial, is likely. Partial bilateral carotid occlusion will also give this type of response.

The occlusion of an anterior cerebral artery was usually accompanied by syncope upon contralateral compression, although there was angiographic filling of both arteries above the communicating artery on the compressed side.

Syncope usually did not occur in patients with hemiplegia due to middle cerebral artery trunk occlusion, if a longstanding carotid occlusion was present or if the angiographic (both cerebral and cervical) pattern appeared to be normal In the latter instance, small artery involvement by arteriosclerosis may exist.

One hundred responses have been correlated with angiographic and neurologic findings. Misleading responses occurred in 16 cases. These included the occurrence of syncope in elderly patients with mass lesions, in brain tumor patients when choked disks were present, or when a "sensitive carotid sinus" existed.

In short, digital carotid compression is an aid in the diagnosis of cerebrovascular failure.

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Dispersion of Fluid Materials in Intracerebral Injections

General Observations in Conjunction with Injection Lobotomy and Chemopallidectomy

E. M. Housepian, M.D. and M. Guzman-Lopez, M.D.

THERE IS sparse literature on experimental intracerebral lesion formation by the injection of fluid material, although Carpenter and Whittier[1] have discussed this technic in their careful study of various methods of producing controlled intracerebral lesions in experimental animals.

In the course of performing injection lobotomy and chemopallidectomy, the question of dispersion of fluid material injected into brain tissue has been raised. By employing technics whereby the total mass of injected material can be controlled radiographically, certain observations have been made and confirmed by comparable studies on cadavers.

The technic of injection of a liquid material into the human globus pallidus, as recently outlined by Cooper,[2,3] has not met with universal success, although localization of a lesion in chemopallidectomy has presumably been controlled by placement of a silver clip or drop of Pantopaque through the catheter following intracerebral alcohol injection. When the marking vehicle (0.1 to 0.2 cc. Pantopaque) was initially instilled via catheter into the globus pallidus in six human cases, followed by 0.5 to 0.7 cc. 92 per cent alcohol in a viscid base, the following was observed. In every case there was extravasation of a significant amount of dye upward along the needle tract, despite the fact that injection was made over a 20 to 30 minute period. In two cases, when a second lesion was attempted within 1 cm. of an earlier one, the dye was seen to break directly into the region marked by the earlier procedure, and in one of these there was appearance of the dye in the ventricular system following injection of 0.3 cc. alcohol, despite the fact that the catheter placement was apparently not closer than 1.5 cm. from the lateral ventricle at any point (figure 1). Further injection was, of course, not attempted in this case. These observations could not have been made if the marking fluid had not preceded the injections.

Procaine injection has been used for lobotomy, and the small series reported contains suggestions of a few unsuccessful cases complicated by peripheral-vascular collapse.[4-6] In this group of intracerebral injections for lobotomy effect, larger volumes of material have been injected (2 to 30 cc.). It is felt by some that the lobotomy effect may be obtained by the rapid introduction of a fluid mass into the frontal white matter which, in effect, momentarily separates and thereby defunctionalizes bundles of fibers. With this in mind, saline has been successfully substituted for procaine in injection lobotomy for certain preterminal pain problems.[7]

In conjunction with this latter procedure, 10 to 12 cc. of a weak solution of Diodrast (2 per cent in N/S) was injected into the frontal white matter through a conventional burr hole, with careful cauterization of the pia-arachnoid in an attempt to seal the needle tract from the subarachnoid space. Injections were made through a long blunt 22-gauge needle passed to the floor of the anterior fossa and withdrawn 2.0 cm. In two patients anteroposterior and lateral roentgenograms and tomograms obtained immediately following injection showed that a small amount of material (perhaps 1 to 3 cc.) was visible in a thin, intracerebral pocket and that the rest of the material was found in the subarachnoid space on the orbital surface of the frontal lobe and over the convexity at the sites of penetration of the pia by the needle (figures 2 and 3). This observation was confirmed in two cadavers at autopsy, during which an identical "saline lobotomy" was performed using a solution of methylene blue. In addition to its appearance over the convexity and orbital surface of the frontal lobe, there was accumulation of dye in the subarachnoid space at the base of the brain. Furthermore, one of these injected brains was cut prior to fixation, and it was notable that a longitudinal separation of fibers had occurred by the narrow pocket of dissecting fluid in the direction of the fiber tracts deep in the frontal white matter (the superior longitudinal fasciculus).

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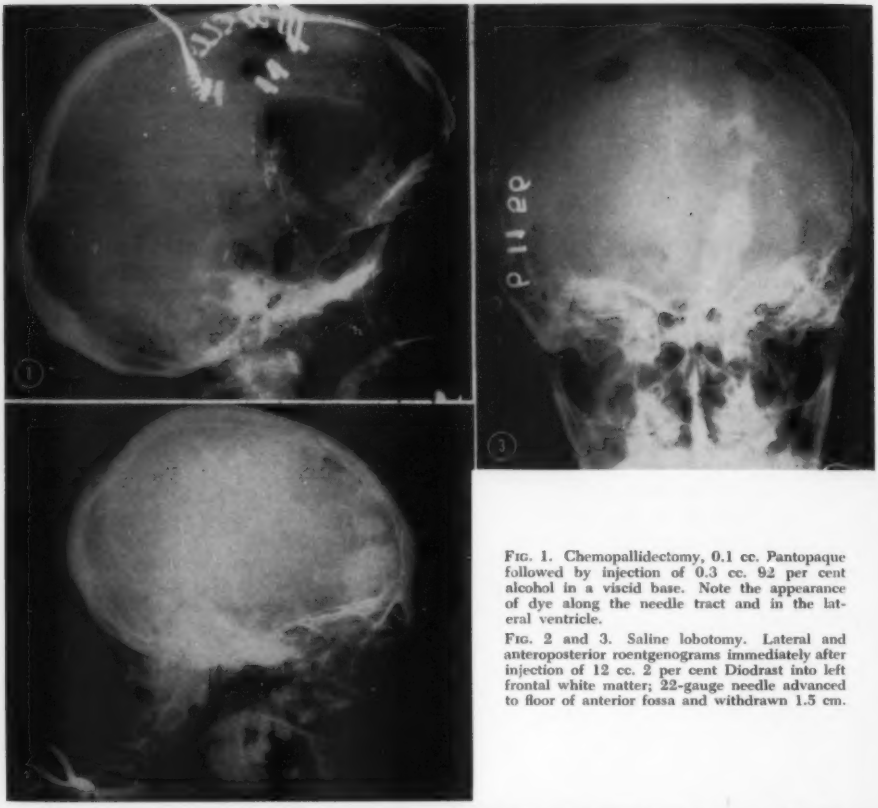

FIG. 1. Chemopallidectomy, 0.1 cc. Pantopaque followed by injection of 0.3 cc. 92 per cent alcohol in a viscid base. Note the appearance of dye along the needle tract and in the lateral ventricle.

FIG. 2 and 3. Saline lobotomy. Lateral and anteroposterior roentgenograms immediately after injection of 12 cc. 2 per cent Diodrast into left frontal white matter; 22-gauge needle advanced to floor of anterior fossa and withdrawn 1.5 cm.

CONCLUSIONS

These observations suggest the following:

1. Fluid material introduced by intracerebral injection through a small-gauge needle will probably form a narrow (1 to 3 cc.) intracerebral pocket, and volumes greater than this amount may dissect along the needle tract and appear in the subarachnoid space, even after cauterization of the pia-arachnoid. For this reason, the use of potentially toxic or harmful agents seems unwise.

2. Even relatively small amounts of necrotizing material introduced by very slow intracerebral injection cannot produce predictable lesions. The injected material tends to seek the path of least resistance, either upward along the needle tract, into an adjacent, previously necrotized area, or it may enter the ventricular system, even though slowly and carefully introduced.

The authors wish to thank Dr. J. Lawrence Pool and Dr. Thomas J. Bridges for their help and encouragement, and Dr. Abner Wolf for his kindness in making available the facilities of the department of neuropathology.

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Electroencephalographic Evaluation of Treatment in Obstructive Disease of the Basilar and Carotid Arteries

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IN RECENT YEARS it has become apparent to the neurologist and neurosurgeon that atherosclerosis of the carotid and basilar arteries is a common cause of neurologic disability and presents an important problem in treatment. Clinical studies of the effects of anticoagulation therapy have been reported by Millikan[1–3] and Fisher[4] in thrombosis and insufficiency of the basilar and carotid arteries and by McDevitt and Wright[5,6] in a group of patients with thromboembolic cerebrovascular disease. In the first two studies the clinical course of a group of patients who received anticoagulation therapy was compared to a similar group who received no treatment.[1–4] In the study reported by McDevitt and Wright[5,6] therapy was intermittent and the clinical course was compared during periods with and without therapy in the same patient. In the three studies it was concluded that anticoagulation therapy tended to prevent transient symptoms due to intermittent insufficiency of the basilar and carotid arteries[1–4] and decreased the incidence of repeated episodes of cerebral embolization and thrombosis.[5,6] Anticoagulation therapy did not appear to significantly alter the course of cerebral infarction once it had occurred.[7]

Since the number of cases is usually small and it is difficult to select an identical group for comparison, there are difficulties in the statistical evaluation of therapy. Furthermore, the practice of intermittent therapy may be hazardous and distort the results, since discontinuation of anticoagulant therapy appears to have resulted in cerebral infarction in some instances.[4,5,7] In addition, there are factors peculiar to the natural history of intermittent insufficiency of the basilar and carotid arteries that must be considered in the evaluation of treatment. Some cases tend to improve spontaneously, and it is not uncommon for repeated attacks of transient neurologic deficit to cease when the patient suffers from cerebral infarction.[9] Any part played by changes in the systemic circulation must also be considered. Transient cerebrovascular symptoms may be caused by failure of the cerebral collateral circulation precipitated by a reduction in cardiac output or a fall in blood pressure.[8–11] Therefore, it seemed worthwhile to compare therapeutic measures designed to maintain the systemic circulation and thereby prevent failure of the cerebral collateral circulation with the effects of anticoagulation therapy.

In order to overcome some of the difficulties in clinical evaluation, a study was undertaken of treatment in 90 cases of occlusive disease of the basilar and carotid arteries by testing the cerebral collateral circulation before and after treatment. The tests used were concurrent recordings of the electroencephalogram, electrocardiogram, and blood pressure, together with any clinical manifestations as the blood pressure was lowered with the tilt-table and during alternate compression of the carotid arteries in the neck. It has been shown previously that patients with carotid artery insufficiency develop abnormalities in the electroencephalogram recorded from the Sylvian region and patients with basilar artery insufficiency develop changes in the electroencephalogram recorded from the occipital regions as a result of postural tilting and that carotid compression causes a more widespread electroencephalographic abnormality. The theoretical background and a detailed discussion of the validity of this test have been reported elsewhere.[9]

MATERIALS AND METHODS

Ninety cases were studied and are summarized in table 1. The sole requirement for selection was that the diagnosis should be well

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Read at the ninth annual meeting of the American Academy of Neurology, Boston, Massachusetts, April 27, 1957.
Present address of Dr. Meyer: Department of Neurology, Wayne University College of Medicine, Detroit, Michigan.

TABLE 1
DIAGNOSIS, AGE, SEX AND MORTALITY ANALYSIS OF TOTAL OF 90 CASES

Total cases studied:		
Basilar artery disease		42
Carotico-basilar artery disease		3
Unilateral carotid artery disease		37
Bilateral carotid artery disease		8
	Total	90
Mean age: 63		
Males: 46 Females: 44		
Deaths:		
Basilar artery disease	8	
Carotid artery disease	5	
Total	13	(14.4%)
Mean duration of symptoms 14 months		
No treatment		9
Dicumarol discontinued within 4 weeks of death		3
Death during Dicumarol treatment	1	(bilateral pneumothorax)

defined and that the clinical data be complete. All cases were examined by at least one of the authors and in many cases by two or more of us. The diagnosis was confirmed by arteriogram or inspection of the affected vessel at operation in 11 cases, by necropsy in five, and by electroencephalogram during postural tilting and compression of the carotid arteries in the neck in an additional 37. In the remaining cases diagnosis was based solely on clinical signs and symptoms, the clinical history and physical examination, including palpation of the carotid arteries in the neck being sufficiently distinctive to allow more than a presumptive diagnosis. A persistent unvarying hemiplegia or hemianopia was assumed to be due to infarction.

The mean period of clinical observation of the 90 cases has been 16 months, but the majority have been observed for two years or longer. The patients were evenly divided between ward and private patients. There were 46 males and 44 females. The mean age for the entire group was 63 years (table 1). The oldest patient was 92 years and the youngest 34 years, but the vast majority were in the seventh and eighth decades. The group was classified according to the vessel principally involved, but the electroencephalogram and arteriography revealed that other vessels were diseased also in some instances. In the entire group of 90 cases there were 13 deaths. A higher proportion of deaths occurred in the group with disease of the basilar arteries than in the group with carotid artery disease (table 1). The mean duration of symptoms prior to death was 14 months in the 13 cases that died, and nine of them received no treatment other than bed rest and general supportive measures. Three cases expired within four weeks after Dicumarol therapy was discontinued because of various contraindications to continued anticoagulation. The remaining patient expired while receiving anticoagulation therapy.

Twenty-three cases received no treatment and constituted a group who were followed prior to our use of therapy with anticoagulants. Many of these cases have been reported previously in another communication;[9] in three of them electroencephalograms were made while compressing the carotid artery and postural tilting at intervals of six, nine, and 12 months for purposes of comparison. Observations of their clinical course were classified into four categories: "improved," "no change," "worse," or "dead," in order to tabulate the natural history of the disease during a mean period of observation for two years. The number and severity of transient ischemic attacks varied from patient to patient. The most severe form of ischemic attack was a transient hemiplegia, the most mild being intermittent blurring of vision. Some patients with severe insufficiency had attacks daily, while others had symptoms at intervals of months. Patients who had complete relief of transient attacks or a reduction in frequency by one-half or more were considered "improved."

Electroencephalograms were made while compressing the carotid artery with postural tilting to 70° in 49 cases before and after various forms of treatment. In addition, carotid arteriograms were made before and after

TABLE 2
NATURAL HISTORY SUMMARY OF 29 UNTREATED CASES

*No treatment: 29 cases**	*Improved*	*Unchanged*	*Worse*	*Dead*
Carotid insufficiency without infarction	1	1	5	2
Carotid occlusion with infarction	3	–	–	1
Basilar insufficiency without infarction	1	2	7	3
Basilar occlusion with infarction	–	–	–	3
Total	5 (17%)	3	12	9

Mean duration of symptoms: 24 months

*Repeated electroencephalograms in three cases with postural tilt and carotid compression at intervals of 6 to 12 months showed progressive deterioration.

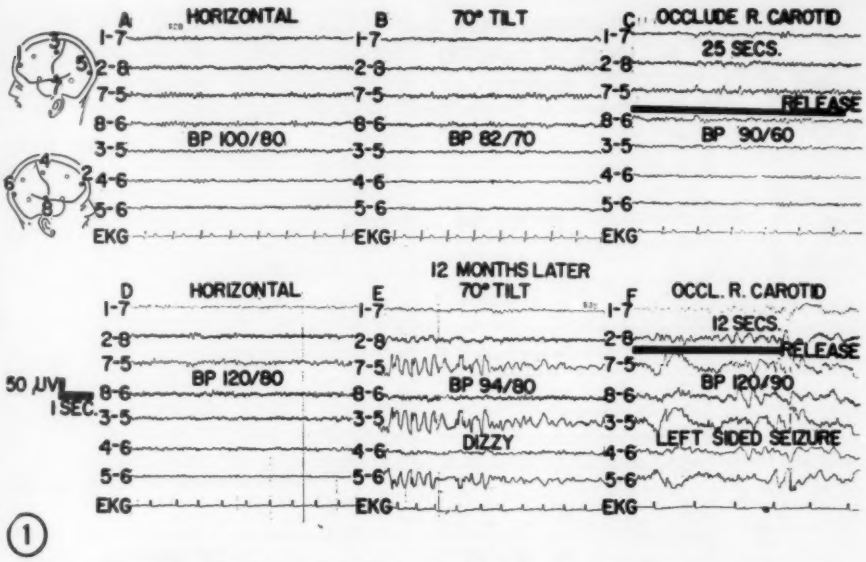

FIG. 1. Electroencephalographic records made during postural tilting to 70° and occlusion of the right carotid artery in a 63 year old man with a two-year history of recurrent episodes of syncope, blindness, dizziness, and ataxia. The first record was made after mild symptoms had been present for one year. The tests showed minimal bitemporooccipital theta activity with right carotid compression for 25 seconds; there was no change during tilt. The second record was made one year later when the attacks were more frequent and severe. Marked bursts of high voltage delta waves appeared in the left occipital and temporal regions with tilting and gross slowing of the electroencephalogram, with a seizure resulting when the right carotid was occluded for 12 seconds.

treatment in three cases of occlusion of the internal carotid artery.

Forty-one cases have been treated with anticoagulation therapy consisting of the intramuscular injection of 100 mg. of heparin every eight hours for two to three days and oral Dicumarol (3,3 methyl bis 4-hydroxycoumarin) in doses sufficient to maintain the prothrombin time between 25 and 35 seconds. The present plan is to maintain the Dicumarol therapy for the rest of these patients' lives, unless some serious contraindication to the use of anticoagulant should arise. In our laboratories a control prothrombin time is 12 to 13 seconds, and 20 to 30 seconds is generally considered to be within "therapeutic range." In 19 of these cases electroencephalograms were made during postural tilting and carotid compression before and after therapy; carotid arteriograms were also made in two cases before and after treatment with Dicumarol for three to five weeks.

Sixteen cases have been treated with ephedrine sulfate administered by mouth in doses of 50 mg. three or four times daily. In nine of these cases, the electroencephalogram with postural tilt and carotid compression was compared before and after the intramuscular injection of 50 mg. of ephedrine.

Five cases of obstructive disease of the internal carotid artery in the neck were selected for surgical treatment.[9,19–22] In two, there was severe stenosis of the internal carotid artery at the carotid sinus, and in the remaining three there was long-standing thrombosis of the internal carotid artery. Arteriograms before and after the surgical reconstruction were performed in one patient, and electroencephalographic testing was performed before and after surgery in the remaining four cases.

RESULTS

Natural History of the Disease. Table 2 summarizes the clinical data relating to 23 untreated cases of obstructive disease of the basilar and carotid arteries who were observed for a mean interval of two years. Seventeen per cent showed spontaneous improvement, the majority of these being patients who recovered from an infarct in the distribution of the carotid artery. In general, patients with

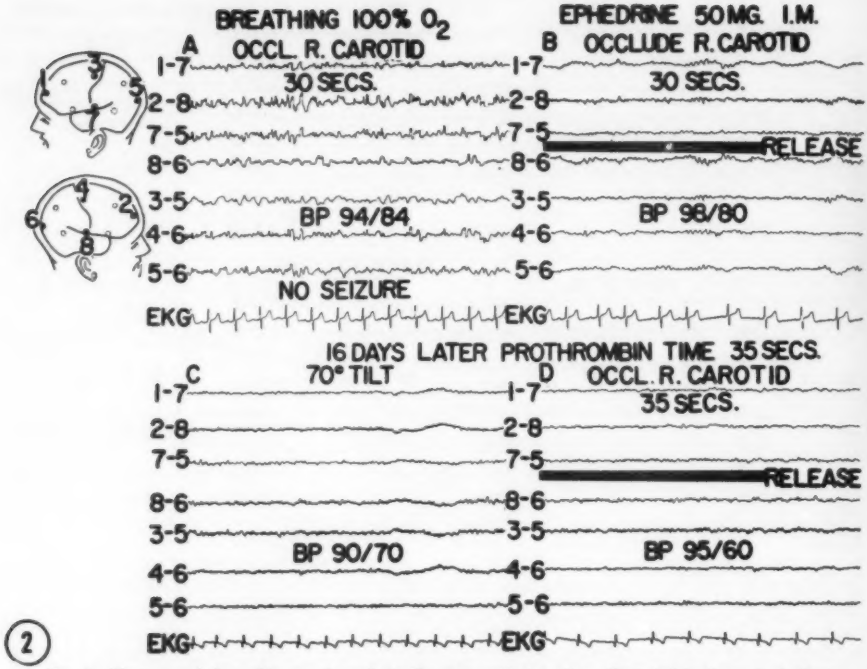

FIG. 2. Electroencephalographic records made in the same patient as those illustrated in figure 1. *A* shows that breathing 100 per cent oxygen prevented the development of a seizure and minimized the electroencephalographic abnormality when the right carotid was occluded for 30 seconds (compare with the same procedure when breathing air, as in figure 1F). *B* shows that the intramuscular injection of 50 mg. of ephedrine prevented the development of electroencephalographic abnormality with carotid compression. In *C* and *D* Dicumarol had been administered for 16 days and postural tilt and compression of the right carotid for 30 seconds failed to produce electroencephalographic abnormality or symptoms (compare with figures 1E and F).

repeated attacks of transient neurologic deficit became worse either because the attacks increased in frequency or because cerebral infarction resulted eventually. In the group of untreated patients 72 per cent were severely disabled or dead within two years.

Comparison of the electroencephalograms during postural tilt and carotid compression in three of these untreated cases at intervals of six, nine, and 12 months showed progressive increase in the electroencephalographic abnormality induced by these tests (figure 1).

Anticoagulation Therapy. Clinical observations pertaining to long-term Dicumarol therapy in 41 cases are summarized in table 3. Although the period of observation in this group is not as long as in the untreated group, comparison of the symptoms before and after treatment showed that 75 per cent were significantly improved and, of the four deaths in the group, three occurred within four weeks of discontinuing anticoagulation therapy. Therapy was discontinued in one case because of severe liver disease, in another because of epistaxis, and in the third in preparation for abdominal surgery. The cause of death in the one patient who died while on anticoagulation therapy was from unrelated, bilateral pneumothorax and mediastinal emphysema. Two additional patients showed marked worsening of symptoms when therapy was temporarily discontinued and improvement when therapy was resumed. The patients showing the most marked improvement were those suffering from vascular insufficiency without infarction (that is, repeated transient ischemic episodes with recovery). Patients who had sustained severe cerebral infarction prior to treatment did not show significant improvement.

In two patients with occlusion of the internal carotid artery, angiography was repeated after three to five weeks of anticoagulation

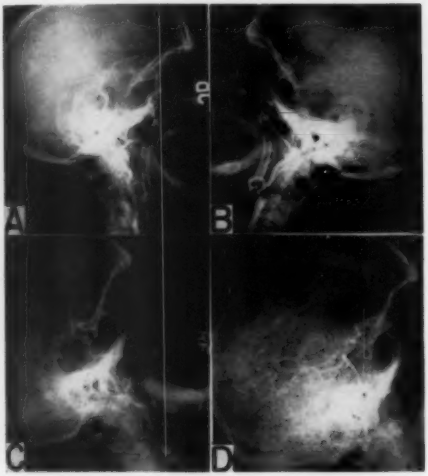

FIG. 3. *A* and *B*, arteriograms made in a 51 year old male with bilateral occlusion of the internal carotid arteries in the neck, resulting in bilateral hemiplegia and coma. *C* and *D*, right carotid and vertebral arteriograms were repeated after five weeks of Dicumarol therapy, at which time he was improved, with appropriate speech and a residual right hemiparesis. Comparison of *C* with *A* shows that 1 cm. of the obstruction has been removed but the internal carotid is totally occluded. Vertebral arteriograms show remarkable filling of all cerebral vessels due to the development of collateral circulation by way of the posterior cerebral arteries.

therapy, during which time clinical improvement had occurred. The procedure was repeated to determine if the obstruction in the vessel had been altered by treatment. In one patient the vessel had become partially patent, but in the other, a patient with occlusion of both internal carotid arteries, 1 cm. of the obstruction had been removed but the internal carotid artery still remained totally occluded (compare figures 3A and C). A right vertebral arteriogram performed after treatment showed filling of both posterior and anterior cerebral arteries by injection of this vessel (figure 3D); the basilar artery was thus supplying both hemispheres by way of the posterior cerebral arteries. The carotid arteriograms showed that the internal carotid arteries received an additional but tenuous supply by collateral flow between the external and internal carotid artery systems via the ophthalmic artery (figures 3A, B, and C).

The results of electroencephalographic testing of the cerebral collateral circulation in 19 patients with carotid and basilar artery disease before and after Dicumarol therapy are illustrated in table 4. In all cases the tests were repeated when the prothrombin time was well within the therapeutic range. After Dicumarol therapy the electroencephalographic abnormality was no longer obtained by tilting or carotid compression in seven cases, was less marked in ten cases, and remained unchanged in two cases. Representative records are illustrated (compare figures 1E and F with figures 2C and D, figures 4B and C with figures 4D and E, and figures 5B and C with figures 5D and E).

The electroencephalographic evidence supports the clinical impression that the cerebral circulation in this group of cases is benefited in some way by anticoagulation therapy.

Ephedrine. Table 5 summarizes the clinical observations in 16 patients treated with oral ephedrine in doses of 50 mg. three or four times daily. The rationale for the use of ephedrine is that it appears to be the most effective drug in the treatment of postural hypotension[9] and is of value in decreasing Stokes-Adams attacks due to changing heart block. Sixty-two per cent of this group were improved by ephedrine. The drug seems to have particular value in those cases with arteriosclerotic heart disease associated with varying degrees of heart block and in cases with postural hypotension. Two of the patients in this group who were not improved by ephedrine therapy after

TABLE 3
CLINICAL EVALUATION OF DICUMAROL TREATED CASES

	Number of Cases	*Mean Duration of Symptoms Prior to Treatment (Months)*	*Mean Duration of Treatment (Months)*	*Improved*	*Unchanged*	*Worse*	*Dead*
Carotid insufficiency without infarction	19	15	8	14	4	–	1*
Carotid occlusion with infarction	5	3	3	3	1	1	–
Basilar insufficiency without infarction	14	6	6	13	–	–	1
Basilar occlusion with infarction	3	5	1	1	–	–	2*
Total	41			31(75%)	5	1	4

*Treatment discontinued

TABLE 4

ELECTROENCEPHALOGRAM WITH 70° POSTURAL TILT AND CAROTID COMPRESSION COMPARED BEFORE AND AFTER ANTICOAGULANT THERAPY*

	Number of Cases	Mean Duration of Treatment	Mean Prothrombin Time	Electroencephalographic Tests Normal	Improved	Unchanged
Basilar artery disease	6	13 days	31 sec.	4	2	–
Carotid artery disease	13	10 days	32 sec.	3	8	2
Total	19			7	10	2

*All electroencephalographic tests before treatment abnormal.

TABLE 5

CLINICAL EVALUATION OF CASES TREATED WITH ORAL EPHEDRINE

	Number of Cases	Mean Duration of Symptoms (Months)	Mean Duration of Treatment (Months)	Improved	Unchanged	Worse	Dead
Carotid insufficiency without infarction	7	16	5	3	1	3	–
Basilar insufficiency without infarction	9	19	10	7	1	–	1
Total	16			10(62%)	2	3	1

six months trial were then placed on anticoagulation therapy with prompt and sustained improvement. Ephedrine does not appear to be as effective as anticoagulation therapy, but its ease of administration makes it a useful therapeutic agent. Table 6 summarizes an evaluation of ephedrine therapy by use of the electroencephalogram with postural tilting and carotid compression. The results of electroencephalographic evaluation support the clinical

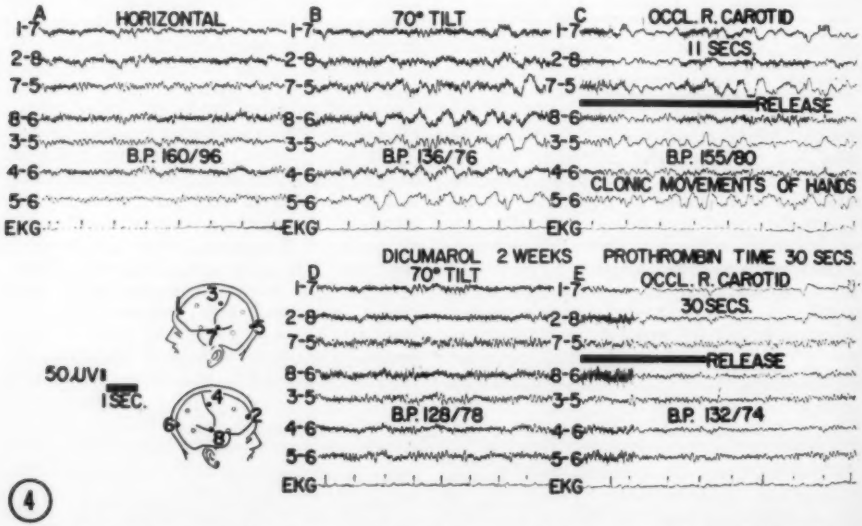

FIG. 4. Sample electroencephalographic records made during postural tilting to 70° and compression of the right carotid artery in a 68 year old male with a one-year history of progressive mental confusion, episodic disorientation, memory loss, impaired vision, and ataxia. There were signs of brainstem damage. Records *A*, *B*, and *C* were made prior to anticoagulation therapy and records *D* and *E* were made fourteen days after the institution of therapy when the prothrombin time was 30 seconds. Postural tilting and carotid compression failed to produce the same electroencephalographic abnormality as prior to therapy and his symptoms had improved. Three weeks later anticoagulant therapy was discontinued because of severe hepatic cirrhosis and he expired one week after therapy was discontinued. At autopsy there was marked atherosclerosis and stenosis of the basilar artery, with a recent thrombotic occlusion and brainstem infarction.

observations. All of the nine patients tested showed less abnormality with postural tilt and carotid compression than prior to treatment. A representative case is illustrated (compare figure 1C with 2B).

Surgical Treatment. Five cases of atherosclerosis of the internal carotid artery in the neck with obstruction were selected for surgery. The results are summarized in table 7. One case with stenosis of the right internal carotid artery associated with repeated episodes of transient left hemiplegia was operated upon with an excellent result. A side-to-side anastomosis of the external to the internal carotid artery was performed in order to bypass the obstruction in the neck. The pre- and postoperative arteriograms are shown in figures 6A and B, and a photograph made at operation of the reconstructed portion of the carotid artery is shown in figure 6C. The patient had a complete left hemiplegia with paralysis of conjugate gaze to the left of one week's duration at the time of operation. Following surgery he made a gradual recovery over the ensuing 14 days. Motor and sensory function returned in the arm before the leg and he now has some residual spasticity of the left side. The paralysis of conjugate gaze is no longer present. He has been observed for 12 months since operation and there have been no further symptoms.

Electroencephalograms made before and after operation showed improvement in the cerebral circulation (compare figures 7B and 7C). When the reconstructed artery was compressed after surgery, the right temporal region showed a marked reduction in amplitude and became isoelectric, and the patient complained of feeling "dizzy" and noticed numbness in the left arm (figure 7D). Electroencephalograms made during compression of the right carotid artery prior to surgery produced no effect.

Another case with stenosis of the right internal carotid artery showed improvement for the first four weeks after surgery, but during the fifth week the carotid pulsation was no longer palpable and the hemiplegia returned. In the remaining three cases the internal carotid artery was found at operation to be obstructed in its entire length from the carotid sinus to the intracranial portion. Thrombectomy was attempted without re-establishing flow and without improvement.

Atropine. A 0.5 mg. injection of atropine subcutaneously has not proved to be of benefit in preventing the appearance of electroencephalographic changes with postural tilting and carotid compression, except rarely in cases of carotid sinus sensitivity.

Nitroglycerin. In one patient whose attacks began when he was treated with nitroglycerin for angina pectoris, the sublingual administration of 0.4 mg. of the drug enhanced the degree of electroencephalographic abnormality produced by postural tilting.

100% Oxygen and 7% CO_2 and Oxygen Mixture. In three cases the electroencephalogram was made while the patient was breathing air and repeated with a mixture of 7 per cent carbon dioxide and 93 per cent oxygen and later while breathing 100 per cent oxygen.

TABLE 6

ELECTROENCEPHALOGRAM WITH 70° POSTURAL TILT AND CAROTID COMPRESSION COMPARED BEFORE AND AFTER THE INTRAMUSCULAR INJECTION OF EPHEDRINE 50 MG.

	Number of Cases	*Electroencephalogram*		
		Normal	*Improved*	*Unchanged*
Basilar artery disease	3	–	3	–
Carotid artery disease	6	1	5	–
Total	9	1	8	–

*All electroencephalograms before treatment abnormal.

TABLE 7

CLINICAL AND ELECTROENCEPHALOGRAPHIC EVALUATION OF SURGICAL THERAPY OF OBSTRUCTION OF THE CAROTID ARTERIES

Diagnosis	*Treatment*	*Blood Flow Re-established*	*Clinical Evaluation*	*EEG Evaluation*
Carotid artery stenosis	External-internal carotid artery anastomosis	Yes	Improved	Improved
Carotid artery stenosis	External-internal carotid artery anastomosis	Temporary*	Partial improvement	Improved
Carotid artery thrombosis	Thrombectomy	No	Unchanged	Unchanged
Carotid artery thrombosis	Thrombectomy	No	Unchanged	Unchanged
Bilateral carotid artery thrombosis	Thrombectomy	No	Unchanged	Unchanged

*4 weeks after operation carotid pulsation absent.

In all cases the electroencephalographic abnormality was less marked when the patient was breathing oxygen or 7 per cent carbon dioxide and oxygen than when breathing air. A representative case is illustrated (compare figures 1F and 2A).

Abdominal Binder and Elastic Stockings. In order to reduce postural hypotension, tight abdominal binders and elastic stockings were placed on four patients before and after postural tilting while recording the electroencephalogram for purposes of comparison. In three of the four patients the electroencephalographic abnormality was decreased.

DISCUSSION

A critical study has been made of 90 cases of insufficiency and thrombosis of the basilar and carotid arteries during a period of observation for two years with a view to gaining information concerning the natural history of the disease and the manner in which its course might be modified by treatment. Clinical observations were correlated with tests of the cerebral circulation under stress which were made in a comparable manner before and after treatment. The test consisted of recording the electroencephalogram during postural tilting and carotid compression.

The data indicate that insufficiency of the basilar and carotid arteries due to atherosclerosis has a natural history characterized by progressive failure of the collateral circulation, resulting in death in 31 per cent of the cases studied and severe disability in an additional 41 per cent occurring within two years of the onset of symptoms. However, there was a wide variability in the rate of cerebrovascular failure from case to case and one patient has survived repeated attacks for a period of seven years. This clinical impression was supported by electroencephalographic testing. Electroencephalograms repeated at intervals of six to 12 months showed a progressive abnormality elicited by postural tilting and carotid compression (figure 1).

Progressive deterioration of the cerebral circulation is assumed to be due to continued

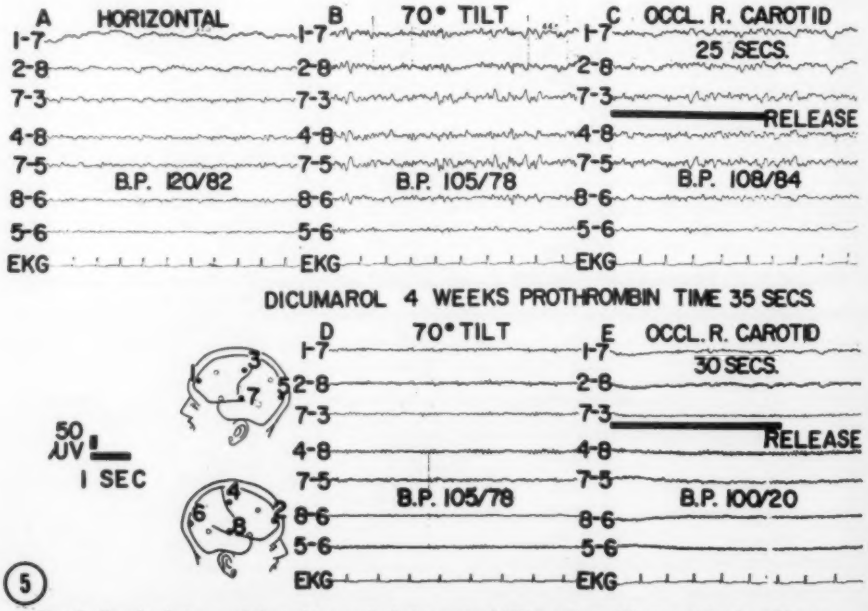

FIG. 5. Sample electroencephalographic records during postural tilting and carotid compression in a 34 year old woman with juvenile diabetes since the age of two and six episodes of alternating and transient hemiplegia ushered in by syncope over a period of eight months. Physical examination revealed signs of damage to both corticospinal tracts and dysarthria. Records *A*, *B*, and *C* were made prior to therapy and records *D* and *E* were made after four weeks of Dicumarol, at which time the prothrombin time was 35 seconds. The patient has had no further attacks while on anticoagulation therapy for 12 months.

atherosclerosis and stenosis of the cerebral collateral vessels, complicated in many instances by associated heart disease and intermittent reduction of cardiac output. This assumption is supported by the high incidence of arteriosclerotic heart disease in the entire group of 90 cases. Symptomatic arteriosclerotic heart disease was present in 36 cases, with myocardial infarction occurring in 12, varying degrees of heart block present in six, and auricular fibrillation present in five. Diabetes was present in eight cases, which is of interest in view of the well known association of diabetes with atherosclerosis. It is assumed that there were more deaths in the group suffering from disease of the basilar artery during the period of study because vital centers of the brainstem are supplied by this vessel. Elsewhere we have indicated the better prognosis in younger age groups.[9]

In considering therapy of cerebrovascular disease it is evident that there are two aspects of treatment that should be considered sepa-

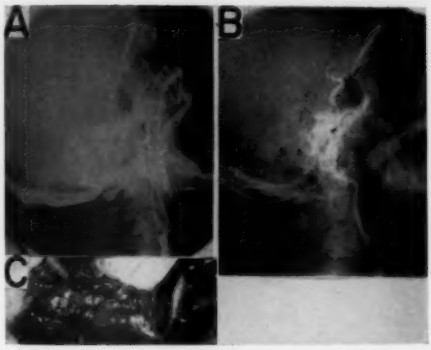

FIG. 6. *A*. Preoperative carotid arteriogram, showing stenosis of the right carotid artery in a 59 year old male who had four attacks of left hemiplegia in an eight week period. *B*. Right carotid arteriogram after anastomosis of the right external carotid to the right internal carotid above the point of stenosis. *C*. Photograph of reconstructed vessel at operation at the site of anastomosis. There have been no further episodes of insufficiency in the year since operation. Some left-sided spasticity persists.

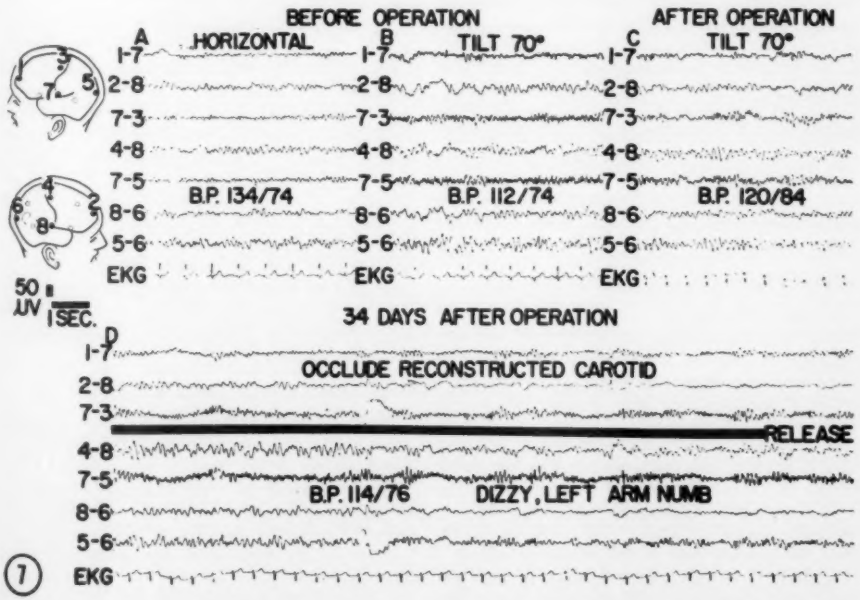

FIG. 7. Samples of electroencephalographic records made in the patient whose arteriograms are illustrated in figure 6. Record *B* was made prior to operation and record *C* was made after surgical reconstruction of severe stenosis of the right internal carotid artery. There is less slow activity induced by tilting in the right temporal region after operation. Record *D* was made 34 days after operation to show that compression of the right carotid artery produced reduction in amplitude of the electroencephalogram recorded from the right temporal region and he complained of dizziness and a numb sensation in the left arm. Compression of the right carotid artery prior to its surgical reconstruction produced no electroencephalographic change.

rately. First, the prevention and treatment of attacks of intermittent ischemia and secondly, the treatment of cerebral infarction. This separation is important because, in general, once cerebral infarction has occurred it is essenitally an irreversible process, whereas cerebrovascular insufficiency is a reversible, physiologic state that is amenable to treatment.[9] In this study, our main concern has been the prevention of intermittent attacks of cerebral ischemia and not the treatment of cerebral infarction.

MAINTENANCE OF SYSTEMIC CIRCULATION

Since local cerebral blood flow is dependent on the systemic blood pressure, the first therapeutic consideration should be maintenance of adequate cardiac output because a transient reduction may precipitate cerebrovascular insufficiency. Heart failure, if present, should be treated with digitalis, and rapid atrial fibrillation should be converted to the most effective rhythm possible. Intermittent and variable heart block and postural hypotension should be recognized and treated early, ephedrine being the most effective drug in this regard. Digitalis toxicity may occasionally increase cerebrovascular symptoms by causing various degrees of reversible heart block and should be avoided. These clinical observations are supported by testing patients before and after treatment with ephedrine by use of the electroencephalogram. Elastic stockings and a firm abdominal support also minimize postural hypotension, but they are uncomfortable for continuous wear and are often discarded.

POSSIBLE MECHANISMS OF ANTICOAGULANTS

From both clinical studies and electroencephalographic testing, anticoagulant therapy appears to improve the cerebral collateral circulation and reduce the incidence of recurrent cerebrovascular symptoms. It does not, in our experience, benefit cerebral infarction once it has occurred. The mode of action is obscure and is not yet fully understood. The beneficial effect is probably not due to recanalization of the occluded vessel alone, although there is evidence both clinically and experimentally that this plays a part in the beneficial effect.

Carotid arteriograms performed in one patient with a recent thrombotic occlusion of the intracranial portion of the left internal carotid artery before and after therapy with Dicumarol revealed that the vessel had become patent although stenosis remained. It, therefore, seems justified to assume that in man, as in experimental animals, anticoagulants promote recanalization of thrombosed vessels.[14,15]

However, benefit produced by anticoagulant therapy, as judged clinically and by tests with the electroencephalogram, appears to be more rapid than could be accounted for by recanalization alone. In one of our patients serial arteriograms showed that the vessel remained occluded, despite prolonged anticoagulation therapy and clinical improvement (figure 3). Furthermore, in two additional cases surgical inspection of the occluded vessel showed that the site of occlusion was extensively calcified and it seems unlikely that any significant degree of recanalization could occur. For example, figure 8A shows roentgenograms of the neck in a case with calcification of both common carotid arteries. A left carotid arteriogram revealed complete obstruction of the left common carotid artery (figure 8B). Surgical inspection revealed extensive atherosclerosis, with plaque formation at the carotid bifurcation. Beyond this point, adherent propagated clot extended into the intracranial portion of the internal carotid artery.

An additional explanation is that anticoagulation therapy improves the collateral circulation supplied by way of the small arterial anastomoses of the cortex. Experimental studies have shown that these vessels may provide an additional collateral blood flow beyond the circle of Willis.[10,11] Additional experiments now in progress show that when the systemic circulation fails, segmentation, stasis, and hemoconcentration occur, ultimately resulting in endothelial damage. In these experiments it is found that anticoagulation tends to prevent sludging of blood in these small cortical vessels. It is evident that the reduction of platelet adhesiveness by anticoagulants plays a part in this phenomenon.[17]

INDICATIONS FOR SURGICAL THERAPY

With further experience it seems probable that surgical reconstruction of the internal carotid artery in the neck is occasionally a justified procedure in well localized obstruction of the carotid artery.[9,19–22] Eastcott and associates[19] reported success in one patient and we have had success in one additional case. Careful selection of suitable cases is important. At present we believe that the ideal patient should have severe stenosis of the carotid artery rather than complete occlusion, since clot tends to propagate distal to a long-standing complete occlusion. The cases selected for surgery should be free of advanced heart disease.

If extensive infarction has occurred, surgical reconstruction is unlikely to be of benefit. We are now inclined to the view that the ideal procedure is thrombectomy or arterial grafting under hypothermia, since anastomosis of the external to the internal carotid artery may sacrifice collateral communications already existing between the ophthalmic artery and the orbital vessels.

THEORETICAL CONSIDERATIONS IN TREATMENT

Since the immediate effects of acute cerebrovascular insufficiency are mediated by ischemic anoxia, oxygen therapy with or without the addition of 7 per cent carbon dioxide is indicated during the acute attack. The beneficial effect of oxygen in induced cerebrovascular insufficiency is illustrated by comparing figures 1F and 2A. In this patient occlusion of the right internal carotid artery for 12 seconds produced generalized electroencephalographic slowing and a left-sided seizure (figure 1F). When the procedure was repeated for 30 seconds while breathing 100 per cent oxygen, less electroencephalographic abnormality occurred and there was no seizure. Similar protection was afforded by breathing 7 per cent carbon dioxide. The beneficial effect of oxygen was confirmed by electroencephalography in two additional cases. The reverse effect, namely the production of infarction by severe anoxia, was noted in one patient with occlusion of the internal carotid artery who suffered accidental carbon monoxide poisoning and developed a transient hemiplegia. We have seen an additional case, not included in this series, who developed hemiplegia as a result of exposure to carbon monoxide. Hypoglycemia should also be avoided. We have seen transient hemiplegia occurring in a diabetic during hypoglycemia, with prompt recovery following the intravenous administration of glucose.

In eliciting histories from this group of patients, certain precipitating factors appeared to be causally related to the onset of transient ischemic episodes. These included blood loss, digitalis poisoning, straining at stool, postural hypotension, the use of hypotensive drugs, an unusually heavy meal, and cardiac dysrhythmia. In one patient the attacks began after a lumbosacral sympathectomy was performed for labile hypertension, and in another patient with insufficiency of the basilar artery an episode of blindness occurred as a result of the Valsalva phenomenon produced by a severe paroxysm of coughing. It is presumed that the causally related factor common to all was a transient reduction in cardiac output.

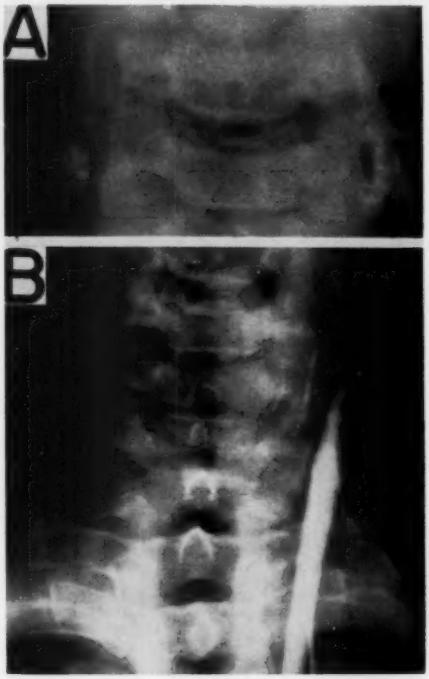

FIG. 8. Roentgenographic studies in a 45 year old male who developed the step-wise progression of a right hemiparesis and dysphasia due to occlusion of the left common carotid artery over a three-week period. Thrombectomy was unsuccessful. He is now symptom-free after anticoagulation therapy for four months. *A*. Soft tissue roentgenogram of the neck at the level of the carotid bifurcation, showing extensive calcification of the internal and common carotid arteries. *B*. Left carotid arteriogram in the same patient to show complete occlusion of common carotid artery.

SUMMARY

Ninety cases of obstructive disease of the basilar and carotid arteries due to atherosclerosis have been evaluated clinically and by use of the electroencephalogram with compression of the carotid arteries and postural tilting, in order to evaluate the natural history of the disease and the manner in which this may be modified by therapy. The disease is commonly characterized in the older age group (in whom basilar and carotid artery occlusion is most frequently seen) by progressive deterioration of the cerebral collateral circula-

tion, complicated in many instances by associated arteriosclerotic heart disease.

Transient episodes of cerebrovascular insufficiency may be decreased in incidence if each case is evaluated separately. Therapy should be directed toward improved cardiac function and avoidance of hypotension, hypoglycemia, and anoxia. During transient ischemic attacks oxygen therapy is beneficial. Ephedrine is helpful in preventing intermittent attacks of cerebrovascular insufficiency, particularly in cases with postural hypotension and variable heart block. Anticoagulation therapy aids in preventing recurrent ischemic episodes in advanced cases where the risks inherent in anticoagulation should be weighed against the hazards of the disease process itself. Surgical reconstruction of severe stenosis of the internal carotid artery in the neck should be considered in carefully selected cases.

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A Clinical Study of 100 Aphasic Patients

1. Observations on Lateralization and Localization of Lesions

Joe R. Brown, M.D. and Josephine Simonson, M.A.

MANY DIFFERENT APPROACHES have been made to the problems of aphasia. The psychologist, the anatomist, the neurologist, and the speech pathologist may examine and each may interpret differently the phenomena seen in aphasic patients. This leads to divergent views and theories concerning aphasia. Also, the literature concerning the subject has been replete with words of considerable length, complexity, and variability. On occasion, an identical word will have greatly different meanings to different disciplines.

TERMINOLOGY

In an effort to overcome some of these difficulties, we have employed an approach using simple terminology that is carefully defined. In our approach, language is considered to consist of four major components, namely, listening, speaking, reading, and writing. "Listening" encompasses all auditory language receptive functions, while "reading" is equated with all visual language receptive functions. The terms "speaking" and "writing" designate the process of formulation and expression of ideas by means of words, phrases, and more complex statements that are spoken or written, respectively. Closely related to these four major components of language are the visual recognition of objects, calculation, motor speech, and the motor act of writing. General conceptual processes, such as the ability to abstract and integrate, as well as special conceptual functions like spacial geometric orientation, also are closely intertwined with language. In similar association, there is the nebulous process variously known as "inner speech" or "symbolic formulation;" one would be inclined to grant its existence but to despair at trying to measure it directly. Specialized forms of language such as chemical formulas, Braille, and sign language need not be considered in most patients.

"Aphasia" is defined as an acquired primary defect of one or more of the aforementioned four major components of language. Use of the word "primary" indicates that the language defect is not secondary to a general intellectual deficit or to emotional upset. The terms "aphasia" and "dysphasia" generally are used to indicate the same clinical condition. The former term has the advantage of long usage, while the latter is more accurate.

PRESENT STUDY

The purpose of this study was to demonstrate the various observed interrelationships between the language defects of patients and the other neurologic deficits, with special reference to the lateralization and localization of lesions. We have attempted to combine the technics of the disciplines of neurology and speech pathology in a clinical study of 100 aphasic patients. Our approach was to record phenomena observed, to allow interrelationships to develop between various phenomena, and to make interpretation only when this appeared to be justified. The omission of certain technics of other disciplines naturally places some bias on our observations and interpretations. Awareness of this bias should be sufficient to enable the reader to evaluate the results presented. Subsequent studies on the same patients will present observations on the basic language defects in these aphasic patients and show how such defects appeared to be modified by the stimulus to language, by the aura of the situation, and by the patients' ways of circumventing the defects.

In the examination of our patients, each component of language was sampled as independently as possible, without requiring the use of a specific second component while testing the first. Thus, when the process of listening was being tested, the patient was permitted to point, gesture, or nod to indicate a correct answer rather than being required to speak. By this approach, it is possible to accomplish a reasonable amount of independent testing of the various components of language. The patients included in this study were chosen from 142 patients who had been examined for possible aphasia during the 12

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months following September 1955. Of these, 18 were not included because of insufficient testing data and 24 were considered not to fit the criteria for the diagnosis of aphasia. The remaining 100 were finally used in this study.

Of these 100 patients, 84 were tested by the Minnesota test[1] and 16 by the Eisenson test.[2] However, in the analysis of data, only those test items were used that appeared to sample each language component as independently as possible. The severity of the defect in each component was graded on the basis of 1 to 4. Thus, a grade 4 defect indicated that the patient missed all or essentially all of the items in the language component tested. In the receptive components of listening and reading, a grade 4 defect would be equated with agnosia.

RESULTS AND COMMENT

General data concerning these 100 patients are given in table 1. Only the data on duration and cause of aphasia need be discussed here.

The patients often showed variability in the degree of involvement in different language components. Only nine of the 100 patients had defects limited to a single component, and the defect was grade 1 in each of these. Sixteen had involvement of two components and 14 had involvement of three components. In half of these patients with involvement of two or three components, the defects were grade 1. The remaining 61 patients had involvement of all four language components. Thus, involvement limited to one language component was uncommon and, when it occurred, the defect was minimal.

Groupings of Aphasic Defects. For some time, while we analyzed our test data, it appeared that there were more differences among patients than there were similarities. Because of this, one is tempted to say that among 100 aphasic patients there are 100 different "types" of aphasia. However, if one accepts rather large general similarities, it became evident that our aphasic patients could be grouped into four chief categories, although further observations on more patients may well change these divisions. The first category included all patients with grade 3 or grade 4 defects of all four language components. We use the term "global" to designate this category. The second group consisted of those in whom reading alone was involved or in whom the reading defect was at least two grades more severe than were the defects in other language components. The third category consisted of patients in whom only speaking or writing or both were involved, or in whom the defects in speaking or writing or both were more severe than those of other language components. The fourth category consisted of the remaining patients and was designated as that of mixed minor defects.

TABLE 1
DATA IN 100 APHASIC PATIENTS

Categories	*Patients*
Sex	
Male	67
Female	33
Occupation	
Business and professional	48
Housewife	29
Farmer and skilled labor	20
Unemployed	2
Student	1
Education (years of school)	
1 to 8	37
9 to 12	33
12+	29
Student	1
Age at onset of aphasia, years	
Under 20	1
20 to 29	4
30 to 39	9
40 to 49	19
50 to 59	25
60 to 69	34
70 to 79	8
Duration of aphasia	
Under 10 days	11
10 to 60 days	33
3 to 11 months	23
1 to 25 years	33

Duration and Cause of Aphasia. Patients were examined any time from three days to 25 years after the onset of aphasia. A total of 44 patients were examined within the first 60 days after onset, 23 in the third through the eleventh month, and 33 after more than a year had elapsed. Each of the four categories of aphasia was represented by patients in each of these three periods. Only one person in the global category was examined formally during the first nine days after onset, because such patients are often inaccessible for detailed studies during that time.

TABLE 2
ETIOLOGIC FACTORS IN 100 APHASIC PATIENTS

Type of aphasia	*Etiologic factor*			
	Infarct	*Mass*	*Other**	*Total*
Global	25	7	0	32
Reading	10	2	1	13
Speaking-writing	13	6	4	23
Mixed minor	20	10	2	32
Total	68	25	7	100

*Posttraumatic (3), convulsive disorder (2), and indeterminate (2).

TABLE 3
ASSOCIATED NEUROLOGIC SIGNS IN 100 APHASIC PATIENTS

Neurologic signs	Type of aphasia: Global (32 patients)	Reading (13 patients)	Speaking-writing (23 patients)	Mixed minor (32 patients)	Total
Minimal or none	3	1	7	13	24
No hemiplegia	5	11	9	16	41
Mild hemiplegia	3	2	9	8	22
Severe hemiplegia	24	0	5	8	37
Cortical anesthesia	4	3	6	5	18
Deep anesthesia	10	0	2	6	18
Hemianopsia	8	11	2	7	28

The relationship between etiologic factors and the aphasic defects is summarized in table 2. There appeared to be no specific relationship between the type of aphasic defect and the cause of the lesion, except for the patients who had reading defects, in whom a relatively small proportion of mass lesions was present.

Associated Neurologic Signs. Some interesting relationships were noted between the type of aphasic defect and other neurologic signs (table 3). The patients with global aphasia most frequently had other neurologic signs, most of which were severe. Patients who had predominant reading defects had the highest proportion of hemianopsia, but their other neurologic signs were the least frequent and least severe. The patients with predominant defects of speaking or writing or both had the highest proportion of the cortical type of anesthesia. Patients with mixed minor defects were similar to those who had global aphasia, except that neurologic signs were often milder and almost half of the group were essentially free of neurologic signs other than aphasia. Three of the 32 patients who had global aphasia had minimal or no signs other than aphasia.

Laterality of Lesions. The relationship between the laterality of a lesion and the handedness of an aphasic patient has been of considerable interest and importance for a long time. The laterality of the lesion was determined in this study by a combination of the history and neurologic signs (other than aphasia), roentgenograms of the head, electroencephalographic findings, and operative procedures. The criteria used to establish laterality necessarily varied from patient to patient. In determining handedness, we used as criteria the hand the patient considered as his preferred hand and the hand he used for most skilled acts other than writing. Table 4 summarizes the data correlating handedness and laterality of lesions.

TABLE 4
LATERALITY OF LESIONS AND HANDEDNESS IN 100 APHASIC PATIENTS

Handedness	Side of lesion: Left	Right	Both	Unknown	Total
Right	79	3	3	4	89
Left	3	1	0	0	4
Ambidextrous	5	2	0	0	7
Total	87	6	3	4	100

In analyzing these data, we omitted those patients in whom the lateralization was bilateral or unknown and considered only the 87 patients with lesions in the left hemisphere and the six patients with lesions in the right hemisphere. The lesion was in the left hemisphere in 94 per cent of these 93 patients. Left-handed and ambidextrous patients composed 9 per cent of those with aphasia caused by a lesion in the left hemisphere, which is close to the incidence in the general population.[3] Exactly half the patients with aphasia resulting from lesions of the right hemisphere were left-handed or ambidextrous, which is far greater than the percentage of left-handed and ambidextrous persons in the general population. The probability of this occurring by chance is less than one in 100.

An analysis of the data on the basis of handedness gives a somewhat different perspective. Aphasia was caused by lesions in the left hemisphere in 96 per cent of the right-handed patients, whereas such lesions were present in 73 per cent of the left-handed and ambidextrous patients.

It is possible to make some limited generalizations on the basis of these data. In patients with aphasia, regardless of handedness, the great probability is that the causative lesion will be located in the left hemisphere. Among right-handed patients it can be predicted with near certainty that the lesion producing aphasia will be in the left hemisphere. The predictability among left-handed and ambidextrous patients is less certain, but there is still a great likelihood of the lesion being in the left hemisphere. Left-handed and ambidextrous patients are considerably more likely to have aphasia due to a lesion in the right hemisphere than are right-handed patients.

TABLE 5
TYPE OF APHASIA RELATED TO LOCUS OF LESION IN 100 APHASIC PATIENTS

Type of aphasia	Total localized	Locus of lesions: I No.	%	I and II No.	%	II No.	%	II and III No.	%	III No.	%	IV No.	%	Unknown
Reading (13 patients)	13	0	0	0	0	2	15	1	8	7	54	3	23	0
Speaking-writing (23 patients)	21	1	5	8	38	9	43	3	14	0	0	0	0	2
Mixed minor (32 patients)	29	1	3	5	17	14	48	9	31	0	0	0	0	3
Global (32 patients)	31	1	3	10	32	4	13	13	42	2	6	1	3	1
Total	94	3	3	23	24	29	31	26	27	9	10	4	4	6

Six of our patients had aphasia caused by lesions in the right hemisphere. All four categories of aphasia were represented among these six patients. In one of the patients with grade 2 to grade 3 involvement of all language components, the defects persisted for at least eight months. Because the number observed is small, this problem requires further study. However, so far in our series, clear differences have not been demonstrated in the aphasic symptoms due to lesions in the right or the left hemisphere, or in right-handed, ambidextrous, or left-handed patients.

Localization of Lesions. The localization within a hemisphere of lesions producing aphasia has been the subject of considerable controversy. In an effort to gain some information concerning this, we studied the correlation between the type of aphasia and the locus of the lesion. The locus of the lesion in the involved hemisphere was determined independently and without knowledge of the specific aphasic phenomena of any of the patients and on the basis of the best information available in each patient. Minimal information in all instances included the clinical history, the neurologic examination, studies of the fundus, measurement of visual fields, and roentgenograms of the skull. Additional information was obtained in many patients from electroencephalograms, pneumoencephalograms, ventriculograms, angiograms, and surgical exploration. In only one case were necropsy data available.

The loci were numbered for convenience as follows (figure 1): I, anterior temporal-posterior frontal; II, midtemporal-anterior parietal; III, posterior temporal-posterior parietal; and IV, anterior occipital. The category of "unknown" was utilized when information was not adequate for accurate localization. The accuracy of the clinical localization of these lesions is open to question; a somewhat comparable study of localization has indicated that each of the various sources of information for localization has an accuracy varying from 81 per cent for the clinical examination to 95 per cent for surgical exploration.[4] By using a summation of various bits of evidence, we believe that our accuracy of localization lies somewhere between these two percentages. It is important to emphasize that by the word "locus" we imply a lesion involving a certain general mass of brain rather than specific "cortical areas." In a number of instances, the evidence indicated that the lesion was large and implicated more than a single "locus." Such lesions were designated as involving, for example, loci I and II. Three patients had bilateral occipital lesions, more extensive in the left hemisphere than the right; these were included in locus IV.

The relationship between the type of aphasia and the locus of the lesions is summarized in table 5. Only three patients had aphasia due to a lesion that appeared to be limited to locus I. In 49 of the 100 patients, the lesion appeared to be large enough to encompass two loci, either I and II, or II and III. Adequate evidence for accurate localization was absent in six patients.

TABLE 6
TOTAL LOCI INVOLVED (SINGLY AND COMBINED) IN 94 APHASIC PATIENTS WITH LOCALIZABLE LESIONS

Type of aphasia	Total localized	Total loci involved: I No.	%	II No.	%	III No.	%	IV No.	%
Reading	13	0	0	3	23	8	61	3	23
Speaking-writing	21	9	43	20	95	3	14	0	0
Mixed minor	29	6	21	28	96	9	31	0	0
Global	31	11	35	27	87	15	48	1	3

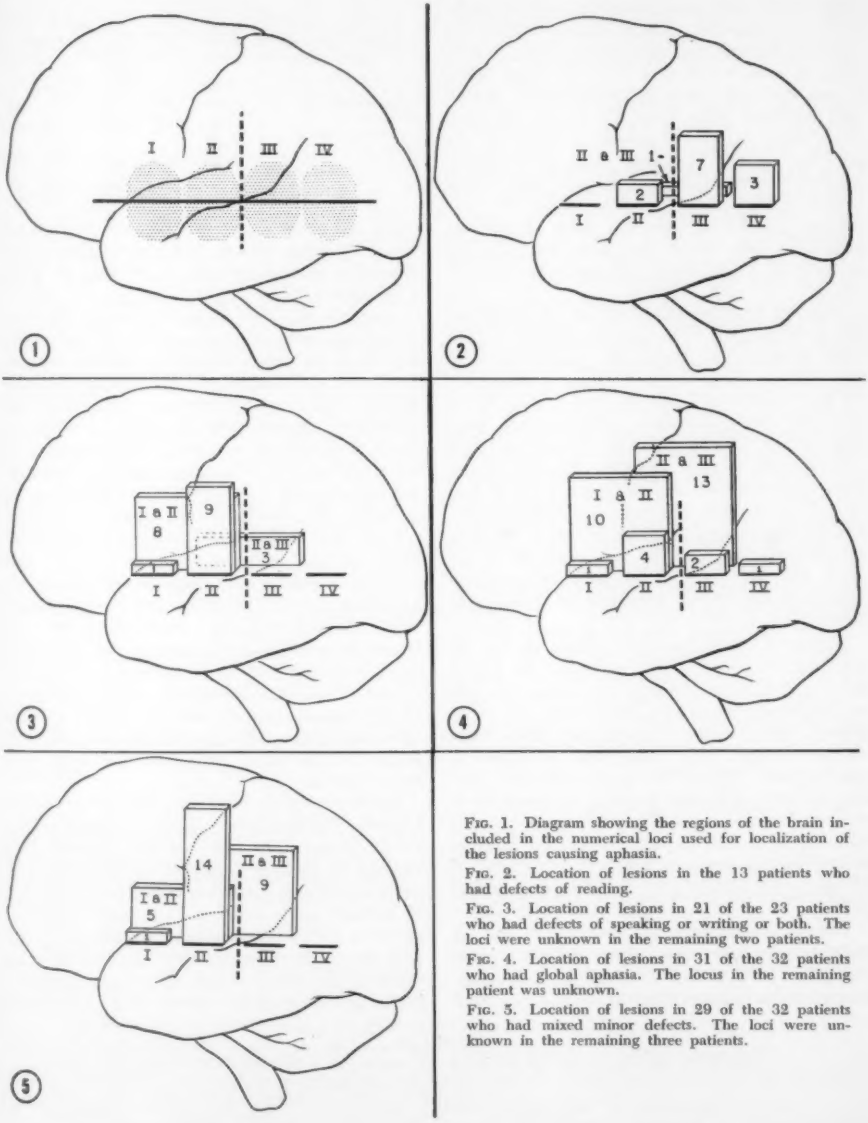

FIG. 1. Diagram showing the regions of the brain included in the numerical loci used for localization of the lesions causing aphasia.

FIG. 2. Location of lesions in the 13 patients who had defects of reading.

FIG. 3. Location of lesions in 21 of the 23 patients who had defects of speaking or writing or both. The loci were unknown in the remaining two patients.

FIG. 4. Location of lesions in 31 of the 32 patients who had global aphasia. The locus in the remaining patient was unknown.

FIG. 5. Location of lesions in 29 of the 32 patients who had mixed minor defects. The loci were unknown in the remaining three patients.

Patients with predominant defects of reading are represented graphically in figure 2. It is apparent that ten of the 13 patients in this group had lesions involving locus III or IV. Of the remaining three patients, one had involvement of loci II and III, whereas two had lesions in locus II.

Table 6 gives data on the 94 patients in whom accurate localization of lesions could be made. It is based on the total number of

times each locus was involved, either singly or in combination. For example, among the 13 patients with predominant reading defects, locus II was involved a total of three times, it was the only locus in two patients, and it was involved with locus III in one patient. Thus, locus III was involved in a total of 61 per cent of the patients with predominant reading defects, and locus IV was involved in a total of 23 per cent of them. Therefore, the lesions associated with this type of aphasia implicated one of the two posterior loci (III or IV) in 11 of these 13 patients (84 per cent).

Patients with predominant defects of speaking or writing or both are represented graphically in figure 3. The locus was unknown in two of these 23 patients. Of the remaining 21, 18 had lesions of locus II, loci I and II, or locus I. This indicates a more anterior location of the lesions than in the group with predominant reading defects. The remaining three patients had lesions encompassing loci II and III. In only one patient in this category did the lesion appear to be limited to locus I. Involvement of locus II was common to 20 of 21 (95 per cent) of the patients with predominant defects of speaking or writing or both.

Figure 4 illustrates the findings in the 32 patients who had global aphasia. In 23 of these patients, the lesions were large enough to encompass two loci, thus indicating that global aphasia often is associated with more massive lesions. The locus was unknown in one instance. The lesions apparently were limited to locus I in one patient, to locus II in four patients, to locus III in two patients, and to locus IV in one patient. As shown in table 6, the lesions involved locus II in a total of 87 per cent of the patients who had global aphasia.

Figure 5 illustrates the findings in the 32 patients who had mixed minor defects. As in the group with global aphasia, the lesions appeared to be concentrated in locus II (a total of 96 per cent of the group), but there were fewer massive lesions and less tendency for extension toward locus I or III than in those with global defects.

TABLE 7

TYPE OF APHASIA AND SIZE OF LESION IN 94 APHASIC PATIENTS WITH LOCALIZABLE LESIONS

Type of aphasia	*Total localized*	*Small lesion*		*Large lesion*	
		No.	*%*	*No.*	*%*
Reading	13	12	92	1	8
Speaking-writing	21	10	48	11	52
Mixed minor	29	15	52	14	48
Global	31	8	26	23	74
Total	94	45	48	49	52

Analysis of these data correlating the type of aphasia with the locus of the lesion as determined by other clinical evidence can be used only to suggest possible trends because of the small series. However, among those patients with predominant defects of reading, the locus of the lesion was most often in the posterior temporoparietal and anterior occipital region. Among patients with other types of aphasia, the predominant location centered around the midtemporal-anterior parietal region.

Table 7 relates the type of aphasia to the apparent size of the lesion as determined by other clinical evidence. Patients chiefly defective in reading ability usually had relatively small lesions, while those patients with global aphasia had predominantly massive lesions. Defects in speaking or writing or both, as well as mixed minor defects, were associated with approximately equal proportions of large and small lesions.

Review of the data with the locus of the lesion as the focal point gives a somewhat different perspective and has the possible advantage of starting from the vantage point of cause and working toward the effect (table 8). In table 8, as in table 5, it is noted that the posterior loci were relatively heavily weighted with instances of predominant reading defects, whereas the other types of aphasia predominated in lesions of the anterior loci. This table

TABLE 8

LOCUS OF LESION RELATED TO TYPE OF APHASIA IN 100 APHASIC PATIENTS

Loci of lesion	*Patients*	*Type of aphasia*							
		Reading		*Speaking-writing*		*Mixed minor*		*Global*	
		No.	*%*	*No.*	*%*	*No.*	*%*	*No.*	*%*
I	3	0	0	1	33	1	33	1	33
I and II	23	0	0	8	34	5	22	10	43
II	29	2	6	9	33	14	48	4	13
II and III	26	1	4	3	11	9	34	13	50
III	9	7	77	0	0	0	0	2	22
IV	4	3	75	0	0	0	0	1	25
Unknown	6	0	0	2	33	3	50	1	17

also re-emphasizes the observation that lesions in any of the loci can be associated with global aphasia. Thus, even if one knows reasonably well the location of the lesion producing aphasia, it is not possible to predict the type of aphasia with any uniformity.

SUMMARY AND CONCLUSIONS

A study has been made at the Mayo Clinic of the general neurologic and language findings in 100 patients with lesions producing aphasia. Four chief types of aphasia were found, namely reading defects, defects in speaking or writing or both, "global" defects, and mixed minor defects. A defect limited to one language component was uncommon; when it occurred, the defect was minimal.

Regardless of the handedness of the patient, the great probability is that the lesions associated with aphasia will be located in the left hemisphere; this probability was 96 per cent among right-handed patients, whereas it was 73 per cent among left-handed and ambidextrous patients.

Aphasia manifested mainly by defects in reading was often associated with homonymous hemianopsia and most often was caused by relatively small lesions. In 84 per cent of these cases, the lesions involved the posterior temporoparietal or anterior occipital region.

Global aphasia often was associated with severe neurologic signs, including hemiplegia, hemianesthesia, and, at times, hemianopsia. The lesions in 74 per cent of the patients with global aphasia were large. The lesions associated with global aphasia involved the midtemporal-anterior parietal region in 87 per cent of the cases.

Patients with predominant defects in speaking or writing or both often had associated milder neurologic deficits, including mild hemiparesis and hypesthesia for discriminative sensation. Defects in speaking or writing or both were associated with a lesion implicating but not necessarily limited to the midtemporal-anterior parietal region in 95 per cent of the patients. The incidence of small lesions and of large lesions was equal in these patients.

Mixed minor defects were associated with neurologic signs similar to those seen with global defects, except that the signs tended to be milder in degree. The incidence of small lesions and of large lesions also was equal in this group of patients. The lesion apparently involved but was not necessarily limited to the midtemporal-anterior parietal region in 96 per cent of the patients.

This study suggests certain trends regarding lateralization and localization of the lesions in aphasia, but fails to support concepts of any absolute relationships. The loci of lesions are intended to imply involvement of a mass of cerebral tissue in variable depth and do not refer to cortical areas. The number of cases in each category of aphasia in this study is obviously small, and thus the various generalizations must be subject to modification on the basis of further observations.

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■ Both sides of the brain are doubtless automatic, motor and sensory, but one side (usually the left) in most people must differ from the other, since disease of but one side (usually the left) makes a person unable to speak. On one side (usually the left) occurs the "dawn of volition and the cessation of automatic action," which is, Spencer thinks, one and the same thing. I may here say that I do not make a total separation betwixt Perception and Expression by representing one as a complex development of sensation only, and the other of movement only. It is plain that, even in a spectral illusion, there are revived not only ideas of objects or colour, but of distance and solidity, and this necessitates a nascent excitation of the muscular movements associated in vision.

J. Hughlings Jackson in *Notes on the Physiology and Pathology of the Nervous System*, published in 1868.

Spirodon (Tetrantoin): A New Anticonvulsant of the Hydantoin Group

Tracy J. Putnam, M.D. and John Jacobs, M.D.

SINCE THE INTRODUCTION of diphenylhydantoin as a specific anticonvulsant selected on a theoretical basis and tested on laboratory animals, as reported by Putnam and Merritt in 1937,[1] an increasing number of similar drugs have been developed and placed on the market. Some have found wide use and others have been withdrawn. Each addition to the group has permitted control of a few more epileptics, but by now the competition is formidable.

Criteria of effectiveness and safety have not kept pace. Reports of new drugs often fail to present tables of percentages of patients kept seizure-free in the various diagnostic categories. It is now clear that untreated patients whose seizures are of recent origin respond as a group more satisfactorily to any new drug than those who have had seizures over many years, despite the use of a variety of medications. In two recent articles[2,3] an attempt was made to outline a "standard" method of treatment, aimed at determining the optimum drug or combination in the optimum dose for the individual patient. In these papers it was strongly recommended that a new drug should be tried at first only on patients who had not responded to the "standard" treatment with more familiar medicines. If it could then be demonstrated to be effective and safe, it deserved a place in medical practice and might with propriety be used on selected new cases. In one of these articles, also, a method of rapid selection by objective means of optimum medication for the individual patient was described,[3] with the suggestion that it might prove an admirable screening method for new compounds.

EXPERIMENTAL DATA

Spirodon is the name given by the pharmaceutical laboratories to their compound S2-676, whose formula is shown in figure 1. The similarity to diphenylhydantoin is obvious. S2-676 was chosen from a series of analogs as having the highest protective ability and lowest toxicity of the series, comparing favorably with established anticonvulsants. These studies have been reported by Hidalgo, Wilken, and Seeberg[4] and by Hidalgo and Wilken.[5] In mice, rats, rabbits, cats, and dogs, the familiar toxic effects of ataxia and drowsiness, lasting about 48 hours, were the only ones observed.

"By the oral route, no fatalities resulted in mice and rats after doses as large as 12 gm. per kg. Intraperitoneally the LD50 dose was found to be about 5 gm. per kg. Dogs tolerated a single administration of 0.8 gm. per kg. with slight ataxia in one of two dogs. On repeated administration, no change in liver or kidney function could be detected in rabbits receiving 0.5 gm. per kg. five times weekly for two weeks. Groups of young rats given 125, 250, and 500 mg. per kg. daily for five days a week for four weeks showed no inhibition of growth, no significant changes in hematology, and no changes in organ weights when compared to a control group. Microscopic examination of the tissues was negative, except for evidence of a very slight inhibition of cell maturation in the bone marrow at the highest dose level. Acute toxicity experiments were also made on some derivatives of compound S2-676."[4]

"It was found to have significant anticonvulsant potency by both the maximal electroshock seizure pattern test and the Metrazol seizure threshold test. Active doses were well below those producing neurologic deficit, giving conventional protective indices (P.I.) of 5.6 and 3.0, respectively. The minimal electroshock seizure threshold was also elevated (P.I. = 6.1). Possible usefulness in both grand mal and petit mal epilepsy is indicated. Testing was performed in mice, rats, rabbits and cats. The activity of some analogues and derivatives was also investigated."[5]

Thus, laboratory studies suggested that S2-676 might be superior to other anticonvulsants currently in common use.

CLINICAL TRIAL ON OLD PATIENTS

The first group of patients to whom Spirodon was given comprised all of those seen in office practice and at the epilepsy out-patient department of the Cedars of Lebanon Hospi-

From the Neurosurgical Clinic, Cedars of Lebanon Hospital, Los Angeles, Camarillo State Hospital, and the private practices of the authors.

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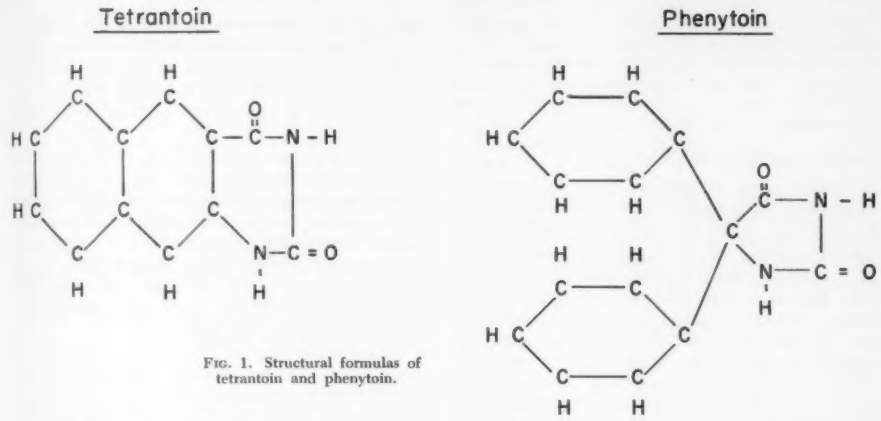

FIG. 1. Structural formulas of tetrantoin and phenytoin.

tal who were not being maintained seizure-free after a protracted trial of the older drugs in maximal doses, according to methods described elsewhere.[2,3] Briefly, these principles are the following:

1. Relatively well known and non-toxic drugs should be preferred to dangerous or untried ones.

2. Treatment should always be started with a well-established drug (usually phenytoin) and others substituted or added only for clear cause.

3. The dose of each drug used should be increased gradually until symptoms of overdosage are produced; then it should be reduced slightly until symptoms of overdosage disappear. As a consequence of this rule, our dosage schedule for most of the common drugs exceeds that usually given in the literature. The median dose of phenytoin in adults is 0.6 gm. daily in our series.

4. Therapeutic trials should be continued until the seizures are under control or until all available drugs have been tried.

5. Adjuvant therapy, such as vigorous exercise, is advised routinely.

SELECTION OF CASES—GROUP 1

The total number of patients still having seizures in spite of rigid application of these principles, on whom Spirodon was given an adequate trial, is 40 (Group 1). They comprise about 35 per cent of all the patients under active treatment.

The patients ranged in age from five to 70 years. Sixteen were children or adolescents and 14 were between the ages of 20 and 35. They were chosen from a group of patients seen in private practice and in the out-patient department of the Cedars of Lebanon Hospital because they were refractory to other drugs, and all were known to us for periods of six months to 15 years before being changed to Spirodon. All had undergone repeated neurologic examinations and electroencephalographic studies; most of them had repeat studies of blood and urine before taking the new drug. In all cases a systematic attempt had been made to give maximum doses of one or more representatives of each group of available drugs.

As an example of the extent to which previous medication was employed, we may cite the case of a married woman aged 46 when last seen in 1955. She had been under the care of one of us since 1945. In 1940, she suffered a "stroke" without obvious cause and was left with a right hemiplegia. As strength returned to the right hand, it began to twitch intermittently, then during most of her waking hours. A surgeon explored her motor cortex and removed a portion. When she recovered from the operation, the spasmodic movements of the right hand were practically constant and extremely severe.

She was given large doses of anticonvulsants as they became available, including phenobarbital up to 2.0 gm. daily, phenytoin to 1.6 gm. daily, and comparable doses of Mesantoin, primidone, trimethadione, Milontin, glutamic acid, amphetamine, and paraldehyde. Of these, phenytoin seemed the most helpful, but she still had frequent focal seizures in the hand and came from New York to California seeking relief.

She had an obvious right hemiparesis and the scar of a boneflap operation over the left parietal area. Electroencephalograms showed a sharp wave focus over the left vertex. Pneumoencephalograms were available, showing an enlarged left ventricle.

She was placed on Spirodon, which was gradually substituted for all of the phenytoin. Eventually she took 2.5 gm. daily. The spasms of the right hand are now only occasional (grade 3) and she is doing her housework and carrying on a reasonably normal life.

DOSAGE AND TOXICITY

In this group of patients, Spirodon was administered as a single daily dose of 0.5 gm., in addition to the medicines the patient was already taking with incomplete success. If it was well tolerated and appeared helpful, the dose was increased by 0.5 gm. weekly until tolerance was reached. The entire dose of all anticonvulsants was usually given at night, as is our general policy.

In all cases, toxic symptoms were deliberately provoked by systematically increasing the dosage until they occurred, usually at a level of 5.0 to 6.0 gm. daily. They consisted of drowsiness, dizziness, ataxia, nystagmus, and nausea. The patient was usually comfortable when the dose was reduced by 1 tablet (0.5 gm.). Eight patients are taking doses over 6.0 gm. daily without symptoms. The majority are comfortable on 2.0 to 3.0 gm. daily.

In 13 cases, however, toxic symptoms occurred at levels of 0.5 to 2.0 gm.—a dose too low to produce therapeutic results in any case.

1. *Rash.* The most troublesome of the side effects were the rashes, seen in eight cases. In most, it was a maculopapular eruption beginning as dull rose colored papules on the trunk and dorsum of the forearm and gradually coalescing to present a beefy-red papular surface. The flexor aspect of the arms, the back of the neck, and the lower legs were spared. In all except two cases, it disappeared within three or four days after discontinuation of the drug. In these cases, however, the rash was more severe, lasting over a week, with fever over 101° F. In one case mild exfoliation occurred. Antihistaminics and corticotropin appeared to be helpful. In many instances of rash following administration of phenytoin or Mesantoin, the rash disappears if the dose is reduced or omitted for a few days, but we could not get any patients who developed rashes re-established on Spirodon. Further attempts should be made, however.

2. *Nausea and vomiting* were severe enough in four cases to cause discontinuation of the drug. No hematemesis, diarrhea, constipation, or cramps were observed.

3. *Confusion* was the rather indefinite but incapacitating complaint in four patients who were unwilling to continue taking the drug.

4. *Fever* was observed in three cases (including the two in which it accompanied a rash). In the third case, the fever did not reappear after a temporary suspension of the drug.

There was no complaint of headache, diplopia, sensitiveness to light, excessive perspiration, unusual growth of hair, or hypertrophy of the gums. The patients did not gain or lose weight to a noticeable extent.

Careful, complete blood counts were done regularly in all cases. In only one case was any significant change observed, and in this case the outcome was fatal.

An unmarried girl of 22 was first seen in September 1953. At that time she complained of recurrent petit mal seizures beginning when she was 12 years old. They occurred several times weekly for a year, then ceased without medication, and then reappeared at age 14. She was placed on trimethadione 1.0 gm. daily, but shortly thereafter she developed grand mal seizures which have continued at the rate of five to six per year up to the time of consultation. The petit mal seizures occurred in groups every one to two weeks. Phenytoin (Dilantin) and phenantoin (Mesantoin) had been tried in maximal doses without effect.

The neurologic and general physical examinations were within normal limits, as were routine laboratory studies. Electroencephalograms and roentgenograms of the skull were normal.

As the patient had come to our care from a distant state and since her seizures rendered her practically an invalid, endangering her attendance at college, a drastic step seemed justified. Since the electroencephalogram was normal, a rapid determination of optimum medication could not be carried out. Accordingly, an intensive or narcosis treatment was undertaken. She was hospitalized with special nurses and given 4.0 gm. of phenytoin daily for four days, with the usual adjuvants and precautions. Her recovery was slower than usual, but she was discharged from the hospital in 20 days. She was given 0.3 gm. phenytoin and 0.3 gm. phenantoin daily when she returned to the care of her local physician.

According to reports from him, she remained seizure-free on this medication until February 1954, when she had two convulsions and from this time on she was never completely free from attacks. Various combinations of medicines were given, including primidone (Mysoline) and phensuccimide (Milontin). In November 1956 she was placed on phenantoin 0.2 gm. and phensuccimide 0.5 gm. As this combination was also ineffective, we suggested that tetrantoin might be added and sent some to the physician in charge. She was put on a combination of tetrantoin 1.5 gm. and phensuccimide 1.0 gm. daily in December 1956, which kept her seizure-free.

Blood counts were taken during all this time at irregular intervals, usually every one to two months. The white blood count had not fallen below 6,000 until May 17, when it was 4,100; the patient remained well.

On June 5, 1957 the patient developed headaches and numerous ecchymoses all over her body, 1 to 5 cm. in diameter. She also had bleeding from the vagina. Her red blood count was 3,500,000, hemoglobin 10 mg., white blood count 2,000 cells, all lymphocytes. All anticonvulsant medication was discontinued and she was treated by transfusions and ACTH. Despite these measures, she went downhill, bleeding 250 cc. per day by vagina. Clotting and coagulation times were normal. The white blood count dropped to 100, bone marrow smears showed a complete absence of cells of the leukocyte series, and she expired on June 19, 1957. No autopsy was performed.

In this case, the agranulocytosis is presumably to be ascribed to the moderate dose of tetrantoin. She had been taking phensuccinimide over a longer period, but no cases of blood dyscrasia are reported from it.

In another case, death from agranulocytosis occurred some weeks after the use of Spirodon was discontinued, apparently attributable to the continued use of acetazolamide. A married woman of 25 was referred to us on October 11, 1954 with a complaint of seizures of 18 months' duration. Each one was followed by a period of confusion of several hours' duration. Her memory became impaired. An electroencephalogram on February 16, 1954 was reported to have shown "epileptic activity with paroxysmal significance and a sharp burst of waves from the right temporal area." Phenytoin, phenobarbital, and phensuccimide had been tried without success. She had just become pregnant.

She was next tried on a combination of phenytoin 0.5 gm. and paramethadione 3.5 gm. daily, but continued having attacks. For financial reasons, she felt unable to have another electroencephalogram performed, but had blood counts monthly. She continued having attacks.

On February 8, 1955 Spirodon was added to the above dosage of phenytoin and paramethadione. Her baby was delivered on March 21, 1955. By April she was taking 2.0 gm. Spirodon, 3 gm. paramethadione, and no phenytoin. The seizures became much milder and were reduced in frequency. The blood count remained normal. On July 13 acetazolamide in a daily dose of 750 mg. was added to the medication in the hopes of controlling the few minor attacks. Spirodon was increased to 6.5 gm. daily and paramethadione omitted.

On September 16 the white blood cell count was 8,850. On October 8 there was a sudden drop in the white blood cell count to 1,000 per cu. mm. Spirodon was omitted at once. On October 10 she began to have bleeding from the gums and was hospitalized by her obstetrician. At this time the white cell count was down to 1,000, the red cell count was 3,300,000, platelets 30,000, and the prothrombin, bleeding, and clotting times were greatly prolonged. She was transfused and supportive measures were administered, but the use of phenytoin and acetazolamide was continued. Profound bone marrow depression was found by sternal puncture.

She responded well to treatment and was considered out of danger. On November 7, 1955 she had a sudden relapse and died.

Autopsy showed a small astrocytoma, 1.3 cm. in circumference, in the left temporal lobe of the brain. The bone marrow was atrophic, showing a cellularity of approximately 3 per cent. The cells consisted of scattered reticuloendothelial cells, many round and scattered lymphoid cells, and a few normoblasts. Myeloid cells and immature megacaryocytes were present. Most of the marrow was occupied by fat. There were fresh hemorrhages into the intestinal tract, lungs, and heart muscle. It was the pathologist's opinion that death was due to acetazolamide poisoning.

RESULTS

Table 1 summarizes these patients according to the symptomatic classification of the seizures. Clearly, the largest proportion of good results was seen in cases in which grand mal was the presenting symptom. The cases of petit mal and psychomotor attacks are not sufficiently numerous to justify more than an impression.

TABLE 1

RESULTS OF USE OF SPIRODON IN 40 PATIENTS UNRELIEVED BY OTHER DRUGS

Still on Spirodon	17	(15 seizure-free)
No longer on Spirodon	21	
Toxic symptoms	14	

Number of Patients with	*Still Taking*	*Stopped*	*Result, Grade*					
			4	*3*	*2*	*1*	*0*	*Toxic*
Grand mal	14*†	15†	15	4	0	1	0	10
Petit mal	0	2	1	0	0	0	1	2
Psychomotor	0	3	1	0	0	0	2	1
Focal	3*	2‡	2	2	0	0	1	1

*In seven cases in which petit mal coexisted with grand mal, both were arrested. In one case in which psychomotor and focal attacks coexisted, only the latter were arrested.

†In five cases, effective only when used in combination with other drugs previously ineffective.

‡One died of intercurrent illness, one of agranulocytosis.

As will be seen, the results were excellent in obviously focal attacks. In 11 additional cases, the seizures, although clinically of the grand mal type, seemed attributable to an injury, encephalitis, or other destructive process. Spirodon was found to be the drug of choice in four of these, but was discontinued in two of the successful cases for external reasons. Five patients with a fairly clear history of encephalitis and mental retardation all did poorly on this, as on other types of medication and the narcosis treatment, but one of normal mentality became seizure-free for the first time.

TABLE 2

SPIRODON—TOXIC SYMPTOMS IN 13 CASES. (Group 1)

Rash	8
Confusion	4
Nausea, vomiting	4
Fever	3
Headache	1
Dizziness	1
Drowsiness	1
Agranulocytosis	1

EFFECT OF TETRANTOIN ON THE ELECTROENCEPHALOGRAM

As is well known, it is usually difficult to detect the effect of therapeutic doses of the usual anticonvulsants on the electroencephalogram, and this has been our experience with tetrantoin, also. It is, however, often possible to select the optimum medication for a given patient by studying the effect of large doses of various drugs on the electroencephalogram—the so-called rapid determination of optimum medication.[3] Tetrantoin was tested in this manner in ten cases (including three in the above 40 cases). It proved the best of those available in four. This is comparable to the results with phenytoin, which was the best in the series in 14 of 47 cases, second best in seven more. Next came phenobarbital, best in nine out of 40 cases, second best in six. The present relative standing of various drugs is shown in table 3.

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TABLE 3

RELATIVE EFFECTIVENESS OF VARIOUS DRUGS

	Dose, Gm.	*No. of Cases*	*Best*	*Second*	*Made Worse*	*"Toxic" Waves*
Phenytoin	1.0	47	14	7	2	0
Trimethadione	2.0	47	4	8	5	1
Mesantoin	1.0	47	4	6	4	2
Phenobarbital	1.0	40	9	6	2	4
Phenacemide	7.5	33	3	0	11	3
Paramethadione	2.0	35	5	4	7	0
AC 268	2.0	27	3	1	5	0
Phethenylate	2.0	20	0	2	4	0
Phensuccimide	3.5	19	1	1	2	0
Glutamic acid	30.0	18	0	2	0	0
Primidone	1.5	17	2	1	3	–
Tetrantoin	6.0	10	4	0	0	0
Celontin	3.0	2	0	1	1	0
Peganone	2.5	2	0	0	0	0
Chlorpromazine	0.1	1	0	0	0	0

	Number of Cases Improved	*Best or Second*			*Best or Second Dysrhythmia Types**				
		GM	*PM*	*Psychomotor**	*1–2 c/s*	*3–4 c/s*	*5–7 c/s*	*spike*	*rapid*
Phenytoin	21	20	2	6	1	6	9	2	2
Trimethadione	12	10	2	1	2	5	4	1	0
Mesantoin	10	3	2	2	0	0	7	1	0
Phenobarbital	15	15	2	3	4	6	7	0	2
Phenacemide	3	3	0	1	1	0	1	0	0
Paramethadione	19	6	1	2	1	5	3	2	0
AC 268	4	0	0	1	1	0	0	0	0
Phethenylate	2	2	0	0	0	1	0	1	0
Phensuccimide	2	2	1	0	0	1	0	0	1
Glutamic acid	2	2	0	2	0	1	0	0	0
Primidone	3	3	2	0	0	2	1	0	0
Tetrantoin	4	4	0	0	0	2	2	0	0
Celontin	2	1	0	1	0	1	1	0	0

*When more than one type was improved in the same case, all are listed.

Hydatid Cyst of the Brain and Its Treatment

B. Griponissiotis, M.D.

ECHINOCOCCUS CYST of the brain is not encountered as frequently in Greece as it is in some other countries where this condition is prevalent. This may be due to failure to recognize the condition, since the neurosurgical service has only recently been organized here. To date 14 cases have been reported from Greece by Patrikios, Coccalis, Carajanopoulos, Sbarounis, Heliades, and Deconomou, and eight cases have been operated upon in the clinic of Maccas. Since 1951 the author has performed 441 intracranial operations, including five hydatid cysts, or 1.1 per cent. In this series there were 305 cases of brain tumor; thus 1.6 per cent of these were hydatid cysts. Three other cases were seen during the period from 1935 to 1942.

One of the reasons why echinococcus cysts are so rare in the central nervous system is that the larvae have difficulty in passing through the capillaries of the liver and the lungs. In fact, since these capillaries serve as a filter which removes these organisms from the circulation, the liver and lungs serve as the most common sites for this disease. Of course, it must be recognized that occasionally the organism may bypass the lungs and reach the brain by way of a patent foramen ovale in the interauricular septum. In other instances, a cyst may rupture in the lung, emptying many scolices into a pulmonary vein. These may then be transported to the brain as well as elsewhere in the body. Another possibility to be considered is the rupture of a primary cyst in the left side of the heart. Such ruptures occur most frequently in children and result in multiple cysts in the brain and in other organs of the body. Figure 1 shows typical multiple cysts within the brain, but in this case necropsy failed to reveal any primary cyst in the heart or any other organ.

Usually echinococcus cysts in the brain are single, but due to the soft non-resistant character of brain tissue they are usually large. Secondary or daughter cysts result from rupture of the primary cyst. This may result from injury to the skull. In one case, in addition to the main cyst in the brain, we found numerous daughter cysts between the dura mater and the bone. These we attributed to injury which caused a rupture of the primary cyst attached to the dura mater.

The cysts within the brain typically have thin walls and are devoid of villi. However, in one of our cases, the wall was very thick and the inner surface contained islets of villi. This abnormality was of the type which Dévé called Cutilôme or Chitonôme. We are indebted to Professor Coutelen whose investigation established the nature of the unusual cyst in our case. He demonstrated the thick, porous wall with islets of villi at intervals upon its inner surface (figure 2).

Echinococcus cysts do not invade the brain but only compress it. The brain, in turn, usually develops a thin gliotic membrane about the cyst, but this is not a true capsule. Hydatid cysts are much more common in children than in adults. This probably results from the fact that children associate more closely with dogs and are not aware of the importance of hygienic and sanitary principles. Seven of our eight cases were children under age ten. The only adult was 45 years old.

The two most common complications of hydatid cysts are 1) secondary infection and 2) rupture of the primary cyst into the subarachnoid spaces or the ventricles with widespread dissemination of the infestation. In our experience echinococcus cysts occur most frequently in the parieto-occipital region. Such was the location in five of our eight cases. The others were in the frontal and frontoparietal regions of the cerebrum or in the posterior fossa.

The clinical picture develops slowly and resembles that of a cystic astrocytoma. Usually the general health of the patient is good and evidence of hydatid cysts elsewhere in the body is uncommon. The most conspicuous symptoms are those of increased intracranial pressure. In children this includes enlargement of the head. Localizing manifestations are mainly hemiplegia and sensory and visual disturbances. Unfortunately, many of these patients lose their vision before the condition is recognized and relieved. Trembling of the extremities may occur and many of our patients suffered from convulsions.

The differential diagnosis is not easily made, particularly in adults where these cysts are usually mistaken for neoplasms. In children

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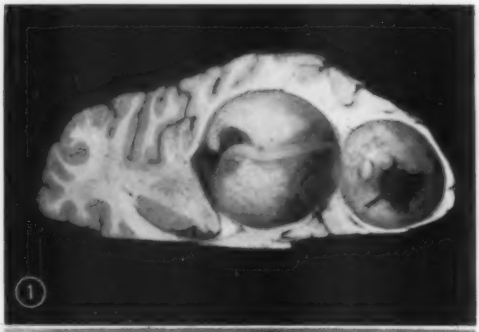

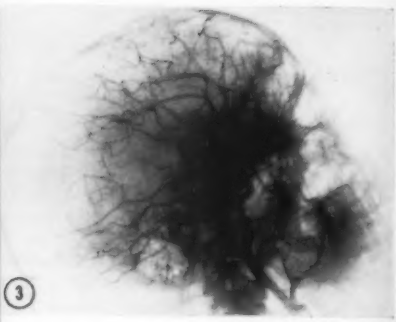

FIG. 1. Multiple hydatid cysts in one cerebral hemisphere.

FIG. 2. The internal surface of the wall of a hydatid cyst.

FIG. 3. Cerebral angiogram made by injecting the dye into the right brachial artery. Note the straight vessels overlying a cyst in the parietal area.

one may suspect the nature of the trouble because of the evidence of cerebral involvement and the presence of convulsions. Ordinary roentgenograms of the skull will reveal evidence of increased intracranial pressure and may demonstrate erosion of the bone overlying the cyst. Unfortunately specific tests such as Casoni's reaction and Weinberg's findings in the blood are not always positive. An eosinophilia is also frequently absent.

Ventriculography is a very helpful diagnostic procedure, but it should be avoided in cases where a hydatid cyst is suspected because of the inherent danger. If the cyst is punctured in the process of making a ventriculogram, one is apt to release the scolices and disseminate the disease widely. If ventriculography is necessary, one should puncture the lateral ventricle on the side opposite the suspected cyst. Cerebral angiography, on the other hand, is a very helpful and a much safer procedure. The important points in cerebral angiography which enable one to both localize and diagnose a hydatid cyst are: 1) the lack of vessels in the region of the cyst and 2) the circular displacement of the blood vessels of the brain about the periphery of the cyst and straightening of the vessels overlying the cyst (figure 3). Because the majority of these patients are children, we make our cerebral angiograms by exposing and puncturing the right brachial artery in the lower third of the upper arm, after the method of Gould. In this way it is possible to outline the entire vascular tree of the ipsilateral hemisphere and, if the opposite carotid is compressed, the circulation of the opposite hemisphere can usually be visualized as well.

Electroencephalography is apparently helpful, as it is in the diagnosis of cerebral tumors, but we have had no experience with it.

The treatment of echinococcus cyst of the brain is surgical. The old method of evacuating the cyst through a small burr hole is not recommended because of the danger of spreading the infestation. The proper method is to remove the cyst intact after making a large osteoplastic craniotomy. The technic outlined by Dowling and Arana and their colleagues is the most satisfactory. After a large osteoplastic flap is reflected, the brain is incised to permit the cyst to escape. The cyst should not be punctured. Arana and San Julian first advocated forcing the cyst from its bed by inject-

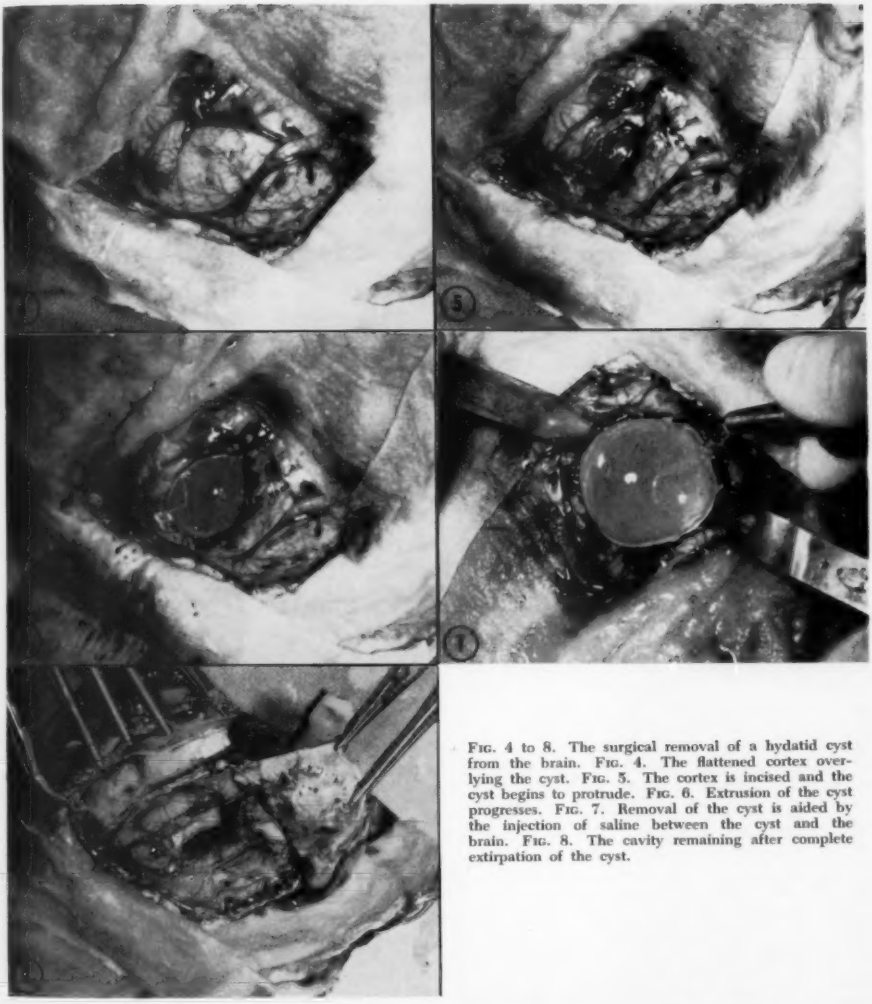

FIG. 4 to 8. The surgical removal of a hydatid cyst from the brain. FIG. 4. The flattened cortex overlying the cyst. FIG. 5. The cortex is incised and the cyst begins to protrude. FIG. 6. Extrusion of the cyst progresses. FIG. 7. Removal of the cyst is aided by the injection of saline between the cyst and the brain. FIG. 8. The cavity remaining after complete extirpation of the cyst.

ing air into the opposite lateral ventricle. Later they found that injecting normal saline between the cyst and the brain was a better procedure. We had arrived at this same technic independently and have used it since 1952. It is our practice to inject normal saline between the cyst and the brain through a metal nozzle (figures 4 to 8). The saline gradually is forced back of the cyst and lifts it from its bed in the brain. This method works well in most cases. For the occasional case where it is not suitable either because the cyst is too large or too deeply situated, it is best to first sterilize the cyst by puncturing it and injecting formalin into it. After the cyst has been emptied, the opening caused by the needle is covered with cotton soaked in formalin. The wall of the cyst is then removed. The cavity left after the cyst has been removed should also be washed with formalin.

In cases where the hydatid cyst has become infected secondarily, it should be treated like

an abscess. After the cyst has been punctured, sterilized, evacuated, and removed, antibiotics should be used.

Frequently the postoperative period is complicated by restlessness and fever during the first few days. Formerly this was attributed to the contents of the cyst which had been spilled during the operation. It is now obvious that this explanation is erroneous, for the same complications may occur when the cyst has been removed intact. Rather it seems that this postoperative state results from the disturbance of the intracranial equilibrium brought on by the removal of this large cyst. Some patients develop a hyperthermia and markedly increased intracranial pressure with protrusion of the operative site. The patient's condition improves following puncture and aspiration of the operative site.

Two of our eight patients died postoperatively, one from infection and one from hemorrhage resulting from an attempt to remove a very thick capsule. This experience demonstrated the inadvisability of trying to remove cysts with thick capsules. One other patient developed Jacksonian seizures which occur at long intervals. Despite the fact that the cyst was punctured in half of our cases either intentionally or accidentally, only one has shown evidence of recurrence. It is our opinion that this favorable situation is the result of the precautions taken to sterilize the contents of the cyst with formalin.

SUMMARY

The problem presented by echinococcus cysts of the brain as it occurs in Greece is outlined. The most effective means of recognition and treatment are described. Eight patients were operated upon, with two deaths, one recurrence, and one patient who developed Jacksonian convulsions.

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■ Drs. Gall and Spurzheim maintain that the brain and cerebellum are originally derived from bundles of fibres contained in the medulla oblongata, and that all the parts of the nervous system, the brain, the cerebellum, and the spinal marrow, are double, and have a common connection by means of commissures, ganglia, or nervous cords, each set of nerves having a connection more or less intimate, according to the particular functions which they are destined to perform. They think that the convolutions of the brain are formed by an union or tissue of diverging and converging fibres, beyond which tissue each duplication may be easily separated into two layers by gentle extension with the fingers, by the injection of water, or by the application of a small but constant force, as in hydrocephalus; and thus the doublings may be evolved into a kind of membranous expansion, covered externally by grey substance. In cases of hydrocephalus, where the brain has been considered as destroyed, the mental faculties remaining, these anatomists assert that the convolutions are not destroyed, but only evolved or stretched.

John Cooke in *A Treatise on Nervous Diseases*, published in 1824.

Neurologic Diagnosis of Pancreatic Islet Cell Adenoma with Hyperinsulinism

J. C. Richardson, M.D. and F. M. Hill, M.D.

IT IS THE PURPOSE of this report to review and classify the neurologic effects of hyperinsulinism in cases of functioning islet cell tumors of the pancreas. It is an important rare clinical disorder with aspects of interest to many diverse specialists, particularly the physician working in metabolic disorders, the abdominal surgeon, and the neurologist. It is one of those conditions in which accurate diagnosis may lead to dramatic surgical cure, whereas failure of recognition results in death or dreadful disability from brain damage. The material here recorded is based chiefly on a review of six selected cases in which there was a verified islet cell tumor of the pancreas.

Knowledge of this subject has accumulated gradually over the last 25 years. In 1922 Banting and Best[1] reported their original work on insulin, and in the same year Fletcher and Campbell[2] described the symptom-complex of hypoglycemia produced by insulin overdosage. In 1924 Harris[3] and others suggested that an identical clinical picture with spontaneous hypoglycemia might be due to overactive or neoplastic islet cells. The first detailed case study was reported by Wilder[4] in 1927, the hyperinsulinism here being due to an islet cell carcinoma with liver metastases demonstrated at operation. The first surgical cure was reported by Howland and co-workers[5] in 1929. In 1933 Whipple[6] described his triad of findings: occurrence of attack with fasting, blood sugar 50 or below during attack, and termination of attack by administration of glucose. This is still recognized as the basis of clinical diagnosis. By 1950 Howard, Moss, and Rhoads[7] were able to review 398 recorded cases of hyperinsulinism due to islet cell tumors. The neurologic signs and symptoms of hyperinsulinism have been noted by many authors, and there are a few reports of the associated neuropathology.

In January 1956 a case of hyperinsulinism due to islet cell tumor was studied at the Toronto General Hospital, and treatment was undertaken before the stage of serious brain damage. This patient presented many of the essential symptoms of organic hyperinsulinism and will be reported. As frequently occurs in these cases, he was referred for neurologic investigation because of spells with loss of consciousness.

CASE REPORT

A 31 year old male factory worker had periodic symptoms typical of a duodenal ulcer from the age of 18, with radiologic demonstration of the ulcer in 1954. In the fall of that year his symptoms recurred and he also began to have episodes of weakness and sweating. In January 1955 he was admitted to a hospital with pyloric obstruction and responded well to gastric suction and intravenous fluids given over one week. On the day these were discontinued he became drowsy and confused and a few hours later had a generalized convulsion. He recovered and a few weeks later a subtotal gastrectomy was performed. Postoperatively intravenous fluids were given for four days. Again on the day these were stopped he became drowsy, confused, had a generalized convulsion, and remained comatose for 24 hours. He was able to leave the hospital a few days later, feeling and eating well.

Over the next year he noted that he frequently felt confused and staggered for about ten minutes after getting up in the morning and for longer periods after a long walk. His wife reported repeated attacks of restlessness with drenching sweats occurring about 1:30 a.m. The patient could not be roused during these episodes and had no recollection of them. His wife also noticed that he was becoming slower mentally and that his memory was very poor at times.

In April 1955 he had a third convulsion after strenuous physical exertion. An electroencephalogram following this revealed a mild frontal abnormality, epileptic in type. In July, following another convulsion, he was started on anticonvulsant drugs, but his symptoms persisted. In August he had to stop work because of increasing fatigue, weakness, and confusion. His job entailed repetitive manual movements and he noted that about midmorning his right arm felt numb and paralyzed, in association with generalized weakness and sweating. When walking his right leg occasionally was affected similarly. His appetite remained good, he gained 20 pounds in weight, and he noted that he could prevent or relieve some of his attacks at work by eating. In December he had another convulsion and was referred for investigation.

Clinical course. The patient was admitted to the medical service of the Toronto General Hospital

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on January 4, 1956. General physical examination revealed no abnormalities apart from flabby obesity and several abdominal scars. He could not remember the details of his history, although his memory improved at times. His speech was consistently slurred. Transient neurologic changes were observed, including hyperactive tendon jerks with Babinski and Hoffman signs on the left on one occasion and on the right during another examination. Skull roentgenograms were normal. An electroencephalogram showed a well organized 10 cps. alpha rhythm interrupted by bursts from the frontal region of five to six cps. waves of twice the alpha voltage. This paroxysmal activity was most prominent during hyperventilation from the frontal regions, but in the transverse run it was more prominent from the left temporal region. A later electroencephalogram showed some irregular paroxysmal slow activity from the frontal regions, particularly on the right side. Fasting blood sugars varied between 76 and 115 mg. per cent (Folin-Wu). An oral glucose tolerance test yielded a diabetic type of curve over the first four hours, with a five-hour level of 92 mg. per cent. With no further oral intake and with vigorous physical exercise, the patient was sweating and fatigued at eight and one-half hours (blood sugar 57 mg. per cent). He then went to bed; at eleven and one-half hours he could not be roused and soon had a generalized convulsion with eyes open and thrashing movements of all four limbs (blood sugar 32 mg. per cent). He recovered immediately with intravenous 50 per cent glucose solution.

A diagnosis of a functioning islet cell tumor was made, and at operation a purplish tumor nodule 1.5 cm. in diameter was found in the head of the pancreas. The insulin content of the tumor was very high and the surrounding pancreatic tissue removed with the tumor revealed hypertrophy and hyperplasia of the islets of Langerhans, with an insulin content twice normal. Postoperatively the fasting blood sugar values leveled off at about 125 mg. per cent, even with a prolonged period of fasting.

CASE SUMMARY

This man's symptoms were noted for one and a half to two years prior to operation. He suffered drowsiness, confusion, coma, and grand mal convulsions. There were episodes of weakness and sweating. He experienced staggering and transient numbness and weakness of the right arm and less often of the right leg. It should be noted that his major convulsions always followed a period of quiet coma. The timing and circumstances surrounding the symptoms are significant. The deeper comatose states with convulsion occurred after stimulation by intravenous glucose in the hospital and after exercise and fasting. The morning wakening symptoms of drowsiness, confusion, and staggering were prominent. In addition to the episodic symptoms, he showed a steady mental deterioration which was only mild and not disabling, however.

REVIEW OF OTHER CASE MATERIAL

In the records of the Toronto General Hospital over the last 20 years, there were only five other cases of functioning islet cell tumors with detailed clinical records. This small group is of no statistical value but does show many important points in regard to diagnosis, clinical course, and treatment. Two of the cases were verified only at autopsy. In one the diagnosis had been missed tragically, in spite of the finding of a low blood sugar during a state of coma. The other fatal case was one reported by Tom and Richardson[8] with wasting and weakness of muscles due to anterior horn cell changes. That patient was a 33 year old woman with hopeless dementia, dysphasia, and paralysis from irreparable cortical damage, so that lack of surgical treatment was no real tragedy.

The other four cases treated surgically include the one reported above, a 20 year old boy with good result apart from troublesome pancreatic fistula, the case reported by Howland and others in 1929 (a 54 year old female with excellent result), and finally a 48 year old woman with considerable residual paralysis and mental impairment.

This last patient is worthy of further mention because she was followed with careful neurologic examinations from the time of her operation in 1938 until 1947. She had presented with spells of trembling, numbness, and light coma, and then more severe attacks with unconsciousness up to six hours. Later she had developed major convulsions and was admitted to the hospital in status epilepticus. It was a routine check of blood sugar with a reading of 33 mg. per cent which led to the correct diagnosis. Postoperatively she underwent a long period of several weeks to regain full consciousness, and she retained weakness of the legs and much mental impairment. When examined two weeks postoperatively she was in a confused, semiconscious state; the neurologist noted weakness in hands and feet and marked wasting of the small muscles of the hands. This led to concern about amyotrophic lateral sclerosis at first, but the wasting and weakness did not progress and, in fact, showed some recovery over the years. She showed a considerable improvement in mentality and speech some years after operation.

Here then is a second case of hypoglycemic amyotrophy undoubtedly related to anterior horn cell changes as in the other case reported by Tom and Richardson.[8] There have been other recent reports of similar cases from London, England, and from the Mayo Clinic. Myelopathic changes with hypoglycemia may prove less rare than previously thought.

The five cases showed features similar to the one reported and some other symptoms such as diplopia, emotional changes, spells of dizziness, and slurring of speech. Episodic psychic changes with strange erratic behavior recurred in several cases. Neurologic findings were prominent in cases with prolonged coma, but the others showed only minor changes such as nystagmus, slight facial weakness, and minor reflex changes.

A review of the major reports in the literature[7,10–17] provides similar data as to clinical symptoms. There is a striking lack of detailed neurologic studies of the cerebral symptoms. It has been pointed out that the frequent milder attacks with weakness, sweating, and trembling are due to hyperadrenalinemia. These symptoms occur with a quick drop in blood sugar in milder hypoglycemic states, including functional as well as organic hyperinsulinism. Other noncerebral symptoms are the feelings of hunger which often occur, the relief of symptoms by food, and the development of obesity.

In this report no attempt is made to survey fully the many possible causes of hypoglycemia, as this has been done well elsewhere. Sometimes the underlying disease such as hepatic cirrhosis may be obscure, but usually there are obvious clinical entities such as Addison's disease, hypopituitarism, and severe liver disease. The hypoglycemia is only secondary in these cases. The neurologic diagnostic problems are presented by those other cases with predominant and isolated hypoglycemic symptoms. It is then a matter of cerebral symptoms, usually episodic, with no overt sign of other causative disease. In such cases the causes of hypoglycemia are fairly well limited to 1) organic hyperinsulinism (islet cell tumor or hyperplasia), 2) functional hyperinsulinism, and 3) factitious hyperinsulinism from secretive injections of insulin. The symptoms of functional hyperinsulinism are relatively mild, with seldom any severe cerebral disturbance. One must be alert to detect cases of factitious hyperinsulinism and to avoid unnecessary surgery. However, such errors are readily avoided if one insists upon satisfactory demonstration of fasting hypoglycemia during hospital investigation.

METHOD OF LABORATORY DIAGNOSIS

The laboratory data necessary for a preoperative diagnosis of a functioning islet cell tumor include repeated demonstration of unequivocal hypoglycemia during the fasting state, hypoglycemia during an attack, and immediate recovery with the administration of glucose.

With an advanced case, routine fasting blood sugar levels below 50 mg. per cent (Folin-Wu), or below 40 mg. per cent by the Somogyi method, may be readily demonstrated, even with a high-carbohydrate diet. With a less advanced case, routine fasting blood sugars may be normal unless severe carbohydrate restriction is enforced. Finally, it has been found that some patients on an inactive hospital routine may be free of attacks despite a day or so of starvation if exercise is not added to the program.

Conn and Seltzer[16] recommend the use of a provocative low carbohydrate, low calorie diet. The patient is given a diet of 50 gm. of carbohydrates, 50 gm. of protein, and 85 gm. of fat (1,200 calories) for three days. Daily fasting blood sugars are taken; if these do not fall below 50 mg. per cent, the patient is fasted on the fourth day. If on the morning of the fifth day the fasting blood sugar is still above 50 mg. per cent, the fast is continued while the patient is exercised vigorously for two hours—for example, on a stationary bicycle—with a final blood sugar determination at the end of that period. The authors point out that where they have failed to demonstrate fasting hypoglycemia by the end of the three-day provocative diet, they have failed to demonstrate it with the additional steps, but they advise that the full program be pursued in an effort both to diagnose early cases and to avoid unnecessary laparotomies. Skillern and Rynearson[15] recommend a 48- to 72-hour fast with exercise. They report that, of 47 patients so tested, only one went over 48 hours without a hypoglycemic attack and on a second test she had an attack at the end of 43 hours.

In functional hyperinsulinism, fasting does not produce hypoglycemia; stimulation by carbohydrate intake is necessary. The situation is similar in alimentary hyperinsulinism in gastrectomized patients. Fasting hypoglycemia occurs in anterior pituitary or adrenocortical insufficiency and severe renal glycosuria and liver disease, but other clinical findings will be

present to distinguish these. A glucose tolerance test is of no use in the diagnosis of functioning islet cell tumors, since almost any type of curve may be obtained.

DISCUSSION

A full understanding of the symptoms of hyperinsulinism depends upon knowledge of the nature and mechanisms of cerebral hypoglycemia. The brain is very dependent upon its supply of oxygen and glucose, suffering neuronal damage with little margin of safety on the deprivation of either. The clinical effects and pathology of cerebral anoxia and hypoglycemia are essentially the same. Higher phyletic levels of the nervous system have the greatest needs and suffer the earliest damage with hypoglycemia. With deepening and receding hypoglycemic coma, one can observe the graded suppression and recovery of functions at the various cortical, subcortical, diencephalic, and brainstem levels. With severe and prolonged hypoglycemic coma, convulsions often supervene and the recovery from the diffuse cerebral arrest is prolonged, with frequent residual focal neuronal damage. The severe encephalopathies from damaging hypoglycemia readily demonstrate these features of diffuse reversible and focal less reversible cerebral damage. The milder recovering hypoglycemic cerebral attacks probably have parallel diffuse effects (on consciousness and mentality chiefly) and varying focal symptoms. The focal effects are chiefly cortical but are also directed to the basal ganglia, brainstem, cerebellum, and even spinal cord.

It is difficult to formulate rigid rules and principles as to when the neurologist must investigate the possibility of hyperinsulinism. Episodic cerebral symptoms of various types must lead to this consideration. It is seldom a matter of simple epileptic attacks of focal or generalized nature, and certainly one need not do blood sugar studies in every case of epilepsy. The convulsive attacks of hypoglycemia tend to occur after preceding coma of minutes or hours duration. With more prolonged symptoms the recurrence of spells of coma or confusion may be replaced by epilepsy which is secondary to cortical pathology. Seizures of various focal types and generalized attacks may occur. Many of the repetitive cerebral symptoms are due to an arrest or depression of cerebral function, rather than to irritability with seizure discharge. Thus one encounters transient paresis, numbness, diplopia, slurring of speech, and so on.

Suspicion of hypoglycemia is strengthened by the timing of symptoms at certain periods of the day, such as the early morning or on awakening. Episodes of erratic confused behavior are common and may be difficult to distinguish from temporal lobe seizures.

Certainly one must consider the possibility of a pancreatic insulinoma in many cases of unexplained coma, and the diagnosis is not uncommonly made by rather routine blood sugar estimations in such cases. The diagnosis becomes a better possibility when a patient gradually emerges from a comatose state showing residual symptoms of cerebral cortical and striatal damage. Recent experience would also suggest that residual skeletal muscular wasting and weakness are not too uncommon.

The following classification of symptoms of hyperinsulinism may help to simplify the problem.

HYPERINSULINISM

I. METABOLIC SYMPTOMS
- (1) Periodic hunger, relief of symptoms by food, progressive obesity.
- (2) Hyperadrenalinemia (from quick drop in blood sugar). Sweating, weakness, tachycardia, inward trembling.

II. CEREBROSPINAL SYMPTOMS
- A. *Episodic.* (Often recurring at set times such as early morning).
  - (1) Cerebral arrest (reduction of neuronal function).
    - (a) Diffuse. Severe prolonged coma (acute encephalopathy). Confusion and other psychic episodes.
    - (b) Focal. Numbness, paralysis, unsteadiness, slurred speech, diplopia, vertigo automatism.
  - (2) Cerebral irritation (epileptic seizure discharge). Often superimposed on coma. Focal or generalized attacks.
- B. *Continuous.* (Chronic neurologic effects)
  - (1) Progressive mild dementia (after many minor episodic symptoms).
  - (2) Severe encephalopathy emerging from prolonged coma. Dementia, dysphasia, paralysis, striatal symptoms.
  - (3) Myelopathy. Wasting and weakness of skeletal muscles.

SUMMARY

A case of islet cell pancreatic tumor with surgical treatment is here presented with particular attention to the neurologic symptoms. Five other verified cases are reviewed.

In discussion of organic hyperinsulinism, the clinical indications and the methods of investigation are outlined.

The nature and mechanisms of the various hypoglycemic cerebral symptoms are described and discussed, and a working classification is proposed.

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■ After passing in review the principal remedies that have been tried in tetanus—opium, bloodletting, the cold bath and cold affusion, ice to the spine, the warm bath, bark, wine and spirits, mercury, purgatives, foxglove, tobacco, musk, prussic acid, carbonate of iron, oil of turpentine, strychnia, woorali, ether and chloroform inhalations, amputation, division of nerves, tourniquets—Sir Thomas Watson says "In all cases, there being no special indication to the contrary, I should be more disposed to administer wine in large quantities, and nutriment, than any particular drug;" and this statement, I take it, expresses a very general feeling in this country. For my own part, I should certainly be more disposed to trust to alcohol than to any drug; but, in saying this, I do not say that I should place no confidence in drugs. I should certainly place no confidence in any sedative or narcotic given by the stomach in sedative or narcotic doses; but, on empirical as well as on theoretical grounds, I should say that opium can scarcely be dispensed with, and that chloroform or ether inhalations will be of infinite service in relieving pain and spasm, and that too without compromising the chances of recovery, if care be taken to pour in wine and to supply nourishment at the same time so as to prevent the patient from waking up almost immediately after the inhalation.

C. B. Radcliffe in *On Diseases of the Spine and of the Nerves*, published in 1871.

CASE REPORT

Tuberculoid Leprosy

Thomas B. Summers, M.D. and George R. Zimmerman, M.D.

LEPROSY was an ancient disease before the dawn of the Christian era. Today it is endemic in Asia, Equatorial Africa, South America, Mexico, and many islands of the South Pacific. In Europe the incidence continues to decline.

The causative organism is *Mycobacterium leprae,* described by Hansen in 1874. The bacillus is straight or slightly curved, measuring three to five micra in length. It is gram-positive and acid-fast. Frequently the organisms collect into compact groups forming "cigar bundles." Koch's postulates have never been fulfilled. Arnold[1] has stated, "There are few bacterial diseases in which the presumably causative organism is as easy to find as it is in the lepromatous form of leprosy, yet there are few in which it is as difficult to find as it is in the tuberculoid form (except during reactions)."

The incubation period may vary from six months to 20 years. The lepromatous type is much more infective than the tuberculoid form. The latter type constitutes 60 to 80 per cent of all cases. According to Doull,[2] 85 per cent of all indigenous cases in the United States are of the lepromatous form. Children are much more susceptible than adults, and among younger age groups contact is an undeniable factor. Lowe[3] makes the statement that there is some evidence that tuberculous infection and B.C.G. vaccination produce some sensitization and immunity to the leprosy bacillus.

In 1948, the International Congress on Leprosy, meeting at Havana, revised the classification of the disease. The lepromatous variety remained unchanged, but the neural form was to be henceforth designated 'tuberculoid' and, in addition, an 'indeterminate' group was added. In the lepromatous variety infiltration of the skin occurs, tending toward nodule formation. Peripheral nerve involvement occurs later in the disease, with resulting neural dysfunction comparable to that of the tuberculoid form. Invasion of the reticuloendothelial tissues, the nasopharynx, upper respiratory passages, and eyes is quite common. The tuberculoid form is characterized by erythematous macules, anesthesia, and loss of pigmentation. Peripheral nerve involvement is early and severe. In active lesions a tuberculoid granulomatous structure is invariably observed.

With neural involvement in either form, atrophy and weakness starting first in the distal portions of the extremities may be observed. Nodular thickening of the nerve trunks may be present, with the ulnar and great auricular nerves showing the highest frequency of involvement. When neural disturbances are the outstanding features, differential diagnosis includes such disorders as syringomyelia, hypertrophic interstitial neuritis, and other neuropathies. Rogers and Muir[4] in their treatise give an excellent discussion on the diagnosis and differential diagnosis of the different types of leprosy.

Chaulmoogra oil has gradually been discontinued in the treatment of leprosy. At the present time the sulfones are foremost on the therapeutic agenda, and some investigators report benefit from dihydrostreptomycin, para-aminosalicylic acid, and, in some cases with complications, ACTH, cortisone, and related steroids. Brand[5] has recently given a review on the role of surgery and physical therapy in the treatment of leprosy.

Recently the authors had an opportunity to examine and study two cases of tuberculoid leprosy. The interest created by these cases prompted this report.

CASE REPORTS

Case 1. This patient, a 14 year old boy, was of mixed racial stock—Caucasian and Polynesian. The only reliable history was obtained through correspondence with the chief of the surgical service at the foreign hospital where the child had undergone treatment for several years. The boy had first been seen in this particular hospital three years before because of two non-healing ulcers on the right leg. Severe weakness of the right lower extremity was observed and the child was able to execute only feeble dorsiflexion at the ankle. There was a complete loss of all sensations below the junction of the middle and distal thirds of the right thigh. The ulcers healed slowly with conservative treatment.

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Two years later, the child received a severe burn on the right foot and was hospitalized four months. The attending physician was unable to explain the cause of the neurotrophic disturbance, but concluded that accidental injection of the sciatic nerve had perhaps occurred during arsenical treatment for yaws. The trophic ulcerations resulting from the burn healed slowly with conservative treatment.

The patient was next seen in the same hospital three months later because of a diffuse cellulitis on the right leg and foot. Roentgenograms of the limb at that time were interpreted as showing arthritis and osteomyelitis of the ankle. The cellulitis subsided and a plaster cast was then applied to the right lower extremity. During this admission, various other diagnostic procedures were carried out. Chest films were normal. Serologic tests for syphilis were negative. There was a moderate anemia, presumably secondary to intestinal parasites. Urinalysis was normal on all occasions.

When first seen at University Hospitals (three years after the onset of symptoms) examination revealed numerous circular scars over the lower trunk and both lower extremities. The nose and mouth were normal. There was an old perforation of the right ear drum. Ocular examination was entirely normal. Examination of the heart and and lungs revealed normal findings. The abdomen and external genitalia were normal. The upper extremities were symmetric and of normal strength. Tests of coordination were normal.

There was swelling of the right ankle, with severe deformity of the foot and toes (figure 1). The skin of the foot was glossy and atrophic; the nails were thickened and deformed. There was pronounced atrophy of the right leg, with a complete loss of ankle dorsiflexion and eversion and toe extension and flexion. Severe sensory impairment existed in the right lower extremity below the distal thigh level. The tendo-Achilles reflex was absent on the right; otherwise, the tendon reflexes were normal. There was no plantar response on the right. The child was able to ambulate fairly well despite this disability, with only minor discrepancies in the gait.

During this first hospital visit, roentgenograms of the right foot and ankle revealed changes compatible with neurotrophic arthropathy (figure 2). Because there was little functional disability, the child was discharged to his home.

The patient returned to the hospital six months later. During the intervening months progression of symptoms had been the course. Examination at this time revealed findings essentially the same as those described previously, except that there was ulceration beneath the base of the fifth metatarsal on the right; the lesion was draining clear fluid. The nails were absent from the second and third toes on the right. Scars were present on the leg and foot from previous ulcerations. The only movement present at the ankle was plantar flexion.

Routine studies of the blood and urine were normal. Serologic tests for syphilis, typhoid fever, and Malta fever were negative. The fasting blood sugar was 93 mg. per cent. Culture of the draining wound revealed hemolytic *Staphylococcus aureus*. Roentgenograms of the right foot and ankle showed further progression of the neurotrophic joint disturbance. Again, treatment was deferred and the child was discharged to his home.

He returned to University Hospitals for the third and final admission three months later. Further progression in the neurologic changes in the right lower extremity was observed. There was a loss of pigmentation of the skin on the distal right thigh at the junction of the middle and distal thirds. At the margin of hypopigmentation on the right thigh, there was a sharp line of demarcation, with sensation severely impaired in the depigmented area and quite normal in the apposing normal skin zone. A 5 cm. area of hypopigmenta-

FIG. 1. *(Case 1)* Inversion of the ankle with adduction of the forefoot. Note the shortening of the great toe and clawing of the small toes.

FIG. 2. *(Case 1)* Roentgenogram of right ankle and foot. The first metatarsal is attenuated and shortened. The bones forming the ankle mortise are fragmented and show sclerotic change.

tion on the left calf was insensitive to pain. Position sense was absent in the toes. Complete spinal fluid studies were normal.

One month later, the ulcer overlying the base of the right fifth metatarsal was excised, including the surrounding skin margins and subcutaneous tissue. Microscopic sections showed chronic ulceration without specific imflammatory reaction. Neither *Lepra bacilli* nor *Spirochaeta pertenue* were found using special stains.

Because leprosy was strongly suspected, a case summary was submitted to Dr. R. R. Wolcott of the U. S. Public Health Service Hospital in Carville, Louisiana, with a request for suggestions regarding further diagnostic studies. On the advice of this consultant, a biopsy of skin and subcutaneous tissue was taken from the right thigh at the junction of normal and abnormal areas of pigmentation.

The specimen was an ellipse of skin and subcutaneous tissue, 5.5 cm. long, 1.5 cm. wide, and 0.8 cm. thick. It appeared normal to naked-eye examination. The entire specimen was sectioned into 3 to 4 mm. thick blocks of tissue, imbedded in paraffin, and microscopic sections were stained as indicated. The tissue was well fixed by formalin when received by the laboratory and bacteriologic cultures were not attempted.

Microscopically the epidermis appeared normal. There was moderate to dense infiltration of lymphocytes around many blood vessels of the dermis and subcutaneous fat and around many of the skin appendages. In several instances, in addition to the lymphocytes, there were small numbers of multinucleated giant cells and spherical masses of epithelioid cells; there was no necrosis in these areas (figure 4).

Close to the deep line of excision, in the subcutaneous fat, a 1 mm. focus of granulomatous inflammation was found. The center of this lesion had undergone caseation necrosis and minimal granular calcification. Around the necrotic debris were a few epithelioid cells. Outside this was a zone of fibrosis and dense lymphocytic infiltration, with an occasional multinucleated giant cell of the Langhans type. There was a remnant of nerve at the periphery of the lesion. Adjacent small nerve branches showed low-grade, granulomatous inflammation similar to that around the blood vessels and the skin appendages (figure 3)

With Ziehl-Neelsen stain (Wade's modification) several dozen acid-fast organisms were seen in each section of the fibrocaseous nodule. The organisms were in the necrotic debris and in a few of the nearby epithelioid cells. They occurred in small clumps or as solitary organisms. Most of the rod-shaped organisms were beaded. There were occasional bipolar forms. The largest organisms were similar in length to *M. tuberculosis;* many were somewhat shorter. Their diameters were equal to those of the tubercle bacilli (figure 5). Sections were stained with Grocott's methenamine-silver nitrate technic;[6] no fungi could be demonstrated either with this stain or with hematoxylin and eosin stains. *M. leprae* were found only in the caseous lesion in the subcutaneous nerve. There were no bacilli in the non-caseating granulomatous lesions around the skin appendages, blood vessels, and small nerve branches.

The child's course while in the hospital was characterized by gradual progression. He limped considerably in walking.

Following biopsy confirmation, Diasone therapy was instituted, the child receiving 0.3 gm. daily, given orally in tablet form. He was kept on the drug until the time of his transfer to the U. S. Public Health Service Hospital in Carville, Louisiana. Throughout the course of this therapy, examinations of the blood and urine were carried out weekly; no significant deviations from normal were ever observed. At all times he maintained an afebrile course; the pulse and respirations were always within normal limits. Progress films of the right foot and ankle showed a steady progression of the joint destruction. X-rays of the pelvis and the right knee were normal.

Progress note. Examination at Carville revealed findings not unlike those described previously. The lepromin test was positive. Amputation of the right leg below the knee was performed and the stump healed per primum. He has been fitted with a prosthesis.

Case 2. This patient, a 14 year old girl, was a full sister of case 1. She was referred to University Hospitals for evaluation because of nodules on the fingers and toes and insensitive atrophic scars on the extremities. Knowledge of the brother's disease had prompted this evaluation by the family physician.

One year before, this young patient had developed a callous on the undersurface of one of the toes of the left foot and similar lesions on the ends of two of the toes on the right foot. One month prior to admission, the fourth toe of the left foot became tender, vesiculated, and later exfoliated. According to the patient, it resembled the type of lesion afflicting her brother. She noticed some numbness of the middle finger of the right hand.

A review of the past medical history revealed measles and mumps during early childhood. She had been plagued with a chronically infected right ear with intermittent drainage. Occasional bouts of gingival bleeding after brushing the teeth had been observed. There was a history of chronic constipation, and worms had been expelled on two occasions in the past five years. In 1949 the child had been treated for yaws with arsenicals and penicillin. At the time of entry to the United States her nutritional state was deplorable and she was a most difficult feeding problem. This later improved.

Physical examination at the time of admission revealed a thin adolescent female weighing 99 pounds. The blood pressure was 95/60. The pulse and respirations were normal. There were nontender small lymph nodes in either anterior cervi-

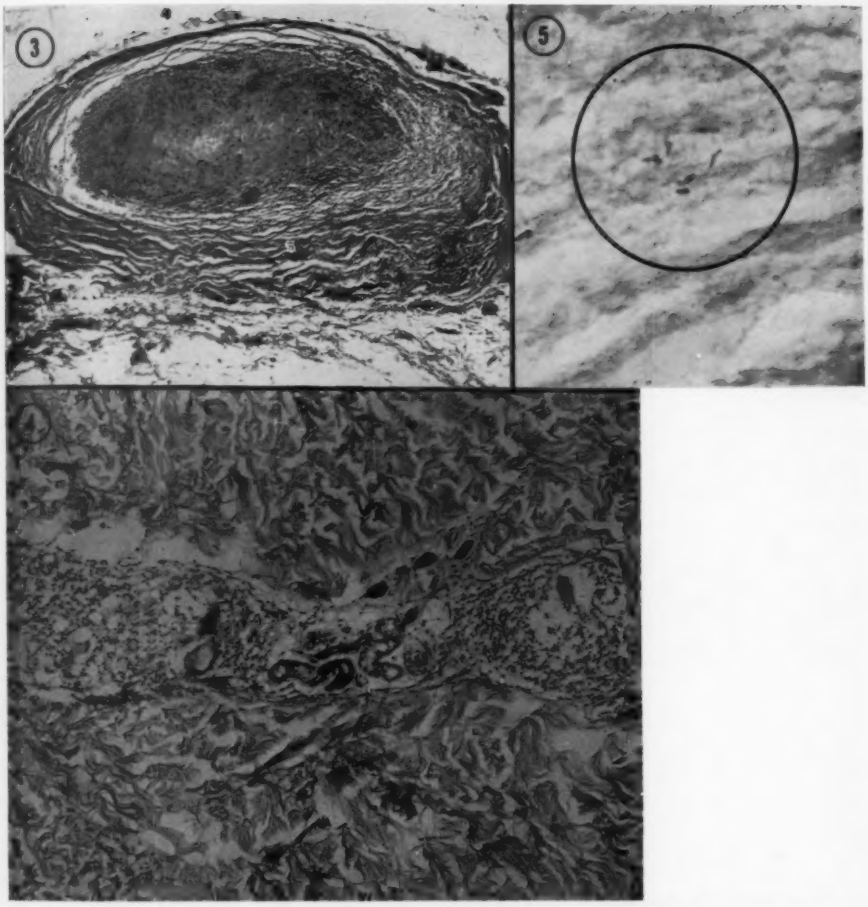

FIG. 3. *(Case 1)* Fibrocaseous granulomatous nodule in subcutaneous nerve. Hematoxylin and eosin stain.
FIG. 4. *(Case 1)* Lymphocytic and multinucleated giant-cell infiltrates around sweat gland in dermis. Hematoxylin and eosin stain.
FIG. 5. Group of *Mycobacteria leprae* in caseous center of lesion shown in figure 4. Acid-fast stain.

cal chain. Ocular examination was entirely normal. Otoscopic examination revealed some scarring of the tympanic membranes. The nose and mouth were normal. Chest expansion was normal and the lungs were clear. The cardiac size was normal; the rhythm was regular and there were no murmurs. The abdomen was normal. Non-tender lymph nodes were palpable in both inguinal regions.

Numerous scars measuring 1 to 3 cm. in diameter were present over the lower trunk and both lower extremities. According to the patient, these had been present since early childhood. These areas of scarring were circular in shape, white in appearance, and atrophic. When the opposing skin edges were compressed the scars would crinkle like tissue paper. All of these scars were insensitive to light touch and pain stimulation.

There was a small non-tender nodule over the distal interphalangeal joint of the right middle finger. The upper extremities were otherwise symmetric and of normal strength. There was slight winging of the left scapula. There was an area of exfoliation on the end of the left fourth toe and the right second toe showed a similar lesion. These areas were quite tender. The left

great toe was foreshortened and deviated upward. There was mild weakness of the ankle dorsiflexors on the right, but strength in the lower extremities was otherwise normal. The tendon reflexes were hypoactive, both in the upper and lower extremities; the superficial abdominal reflexes were normal, as were the plantar responses. Tests of coordination were normal throughout; the station and gait were normal.

In addition to the sensory impairment demonstrated in the pitted scars, examination revealed severe sensory disturbances in the hands and feet pursuing a glove and anklet distribution. In addition there was impairment of sensation in the D5-7 dermatomes on the right.

Routine studies of the blood and urine were normal. Roentgenograms of the chest and both feet revealed normal findings. Stools were examined on several occasions and no parasitic forms observed.

Several attempts were made to demonstrate Hansen's bacillus, with failure on each occasion. Nasal smears were negative. A skin biopsy taken from the left ankle region posterior to the medial malleolus (at the junction of normal and abnormal sensory zones) was normal. Skin and a portion of a digital nerve were removed from the left great toe on the dorsolateral aspect; this, too, was normal. Skin scrapings from the right scapular area were negative for *Mycobacterium leprae.*

Progress note. The child was admitted to the U. S. Public Health Service Hospital at Carville, Louisiana. Examination there revealed anesthesia from the wrists and mid-legs distally. The circular hypopigmented scars were not considered leprous in nature. Skin and nasal scrapings failed to reveal *Mycobacterium leprae.* The lepromin test was positive. A diagnosis of tuberculoid leprosy was based on the history and physical findings. She was discharged to her home with the recommendation that she take Diasone 0.3 gm. daily for an indefinite period of time.

SUMMARY

Two cases of tuberculoid leprosy are reported. In both cases the outstanding features were those of neural dysfunction. The characteristic microscopic findings in one case are presented.

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■ In dealing with the symptoms of myelitis it has been shown that these are very different from those of spinal meningitis—so different as to make it difficult to confound them, if only moderate care be taken in realizing them. In spinal meningitis the most prominent symptom is pain in the back and extremities, produced or aggravated by movement; in myelitis pain of any kind has scarcely a title to be reckoned among the symptoms, pain produced by movement certainly not. In spinal meningitis the sensibility is somewhat exalted, in myelitis it is abolished. In spinal meningitis there is muscular weakness, and the muscular movements are fettered by pain, but there is no true paralysis; in myelitis paralysis is the symptom of symptoms. In spinal meningitis there is a state simulating trismus and tetanus, a state of muscular rigidity half voluntary as to its character, of which the object is to prevent certain movements which give rise to pain; in myelitis the muscles are limber, and there is usually an utter absence of any symptom akin to tremor, convulsion, or spasm.

C. B. Radcliffe in *On Diseases of the Spine and of the Nerves,* published in 1871.

CASE REPORT

Optic Atrophy as an Isolated Sign of Unruptured Carotid Aneurysm

Lowell E. White, Jr., M.D. and Eldon L. Foltz, M.D.

OPTIC ATROPHY as the sole sign of an unruptured aneurysm of the internal carotid artery has been previously reported as a rare occurrence, but the incidence of this lesion appears to be more common than supposed. This suggests that primary, chronic progressive optic atrophy should alert one to the possible diagnosis of internal carotid aneurysm which must be verified by diagnostic carotid arteriography.

These points are illustrated by the following case presentation and a brief review of the recent literature.

CASE REPORT

A 57 year old white female was seen on August 11, 1955 with the chief complaint of failing vision which had begun 15 years prior. The right eye vision loss occurred first and the left eye vision loss appeared ten years later. Her visual defect slowly progressed until February, 1955, when sudden bilateral decrease in visual acuity occurred. This was associated with photophobia and sharp supraorbital pain. She denied diplopia. There was a long past history of anxiety associated with floating sensations, intention tremor, and intermittent numbness and coldness of the hands. No other neurologic symptoms were present.

The patient was an asthenic, tense, white female. Blood pressure was 110/70, pulse 88, respirations 22. The right eye was slightly more prominent than the left. The right pupil was slightly larger than the left. Visual acuity was diminished (O.D. –light and shadows; O.S.–20/200). The direct and consensual light reflexes were brisk bilaterally. The fundi showed smooth, pale, clearly demarcated optic disks, more marked on the right. Visual fields showed only central vision on the right. Moderate constriction was present on the left, with a suggestion of increased temporal loss. The sense of smell was minimally decreased on the right. Her gait was unsteady with bilateral veering, and there was an inconstant, glove-like hypesthesia of the hands. No other neurologic abnormalities were present. Skull roentgenograms showed mild erosion of the anterior clinoid and medial sphenoid ridges on the right. The spinal fluid was clear and under a pressure of 82 mm. The cerebrospinal fluid protein was 47 mg. per cent.

On September 22, 1955, a right carotid arteriogram showed a congenital aneurysm arising from the first segment of the intracranial portion of the right internal carotid artery just distal to the emergence of the artery from the cavernous sinus and immediately proximal to the second curve of the "siphon" (figure 1A and B). It extended superiorly into the posterior portion of the right anterior fossa, lateral to the anterior clinoid, in a position to compress the right optic nerve. On its anterior-superior surface was a daughter aneurysm.

On September 26, 1955, a Selverstone clamp was applied to the right internal carotid artery in the neck and closed during a three-day period with electroencephalographic control. Occlusion of the internal carotid artery supplying the aneurysm was thus achieved. On December 13, 1955, a postoperative arteriogram showed complete occlusion of the right internal carotid artery. Left carotid arteriography showed no filling of the aneurysm with dye, though the remainder of the right hemisphere received adequate collateral blood flow (figure 1C). The patient was subsequently transferred to the psychiatric service for evaluation and treatment of her severe anxiety neurosis.

Follow-up examinations showed a definite improvement in visual acuity during the following year (O.D.–20/200; O.S.–20/70). The visual fields remained essentially stationary (figure 1D). She was otherwise asymptomatic except for photophobia and various psychiatric complaints.

DISCUSSION

Optic atrophy in the present case was a startling finding and suggested a primary chronic retrobulbar neuritis. The slowly progressive nature of the lesion was difficult to evaluate without other signs of disease and resulted in the insidious destruction of the optic pathways.

Intracranial aneurysms located on the internal carotid artery just distal to the ophthalmic artery (C_2 of Ecker)[1] are in an excellent position to compress the optic nerve, yet the clinical significance of such a lesion is seldom stressed in the recent literature. Kennedy[2]

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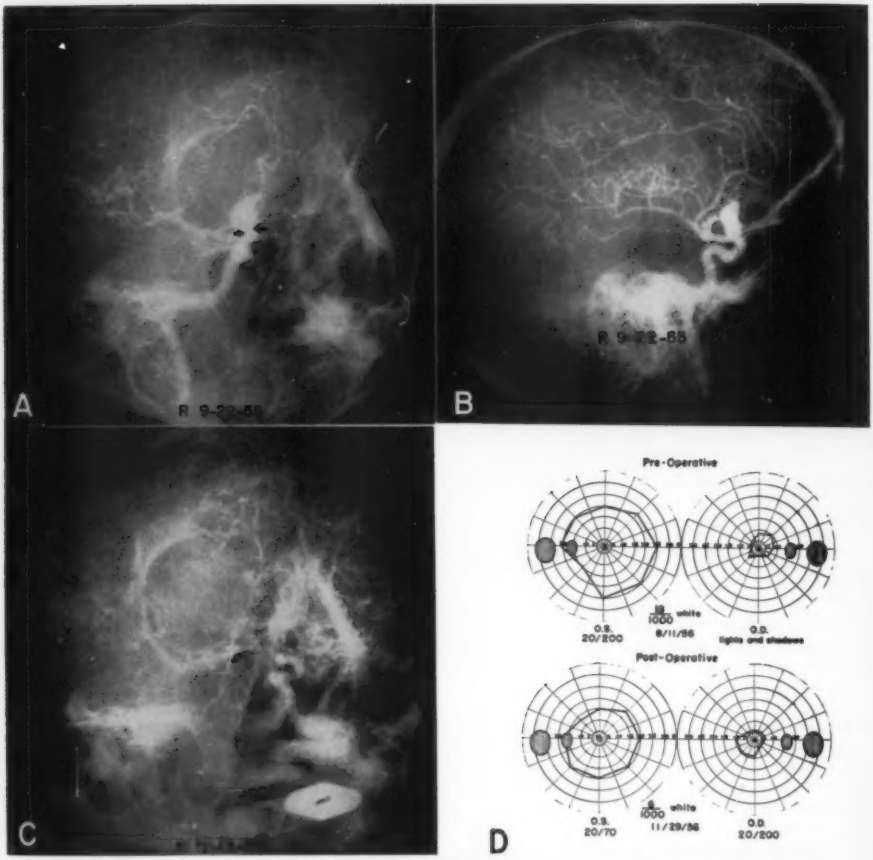

FIG. 1. *A.* Preoperative right carotid arteriogram, right orbital view. *B.* Preoperative right carotid arteriogram, right lateral view (—> <—indicates site of aneurysm). *C.* Postoperative left carotid arteriogram, right orbital view (—> indicates site of aneurysm shown preoperatively). *D.* Pre-and postoperative tangent screen visual fields. Postoperative fields done one year following right internal carotid ligation. Visual acuity improved. No significant change in visual field defects.

recognized its importance when he reported a case of an aneurysm in this area which reproduced the syndrome that bears his name, and both Duke-Elder[3] and Marthinsen[4] have pointed out the lack of emphasis placed upon optic atrophy induced by aneurysms.

Approximately 30 per cent of all congenital intracranial aneurysms arise from the internal carotid artery.[5] In a series of 262 aneurysms, Jefferson[6,7] reported 30 aneurysms which produced optic nerve symptoms. The majority of these originated from the internal carotid artery and 10 per cent showed optic atrophy as their only sign. Fifteen similar cases have recently been reported.[4,8–14] Isolated optic atrophy has also been recorded as a result of fusiform dilatation of the internal carotid artery.[15–19] Ley felt that this type of aneurysmal dilatation is likewise congenital.[20]

The present case illustrates the progression of the disease as well as the dangers of lack of treatment. The sudden progression of symptoms associated with supraorbital pain indicated enlargement of the aneurysm with danger of rupture. This is supported by the arteriogram (figure 1A and B) which shows a

small daughter aneurysm superiorly, presumably the site of the recent enlargement. The sudden enlargement necessitated urgent ligation of the internal carotid artery.

Carotid ligation can improve vision, but the precise events responsible for such improvement are not known. Because of this visual improvement, a partially reversible lesion must be present. Aneurysms have two mechanisms by which they can produce tissue destruction: 1) direct constant compression by the aneurysm mass, and 2) intermittent additional increment of compression by pulsations. It is conceivable that the rich arterial supply to the chiasm[21] was compressed by the aneurysm by these two mechanisms, though the main effect of the pulsatile aneurysm mass was to compress the right optic nerve. This produced bilateral and irregular visual field changes. The rapid improvement in vision following internal carotid ligation (figure 1D) was probably due to loss of pulsatile compression of optic pathways. The subsequent gradual improvement may have also been due to resolution of the thrombosed aneurysm mass.

Such improvement can be achieved by direct intracranial ligation of the aneurysm, but the majority of cases of aneurysms of this type have been treated with internal carotid artery ligation.[2,9,10,22,23] Probably the time of treatment is more important than choice of surgical treatment, for early diagnosis and ligation can result in complete restoration of vision. The prolonged preoperative course in this case and in others reported[4,9,11,22] emphasizes the need for more widespread use of early arteriography in cases of progressing optic atrophy. Even without subarachnoid bleeding or even symptoms of aneurysm enlargement, arteriography may be indicated in order to achieve early diagnosis and treatment, and thus allow maximum recovery of vision.

SUMMARY AND CONCLUSIONS

A case of optic atrophy as an isolated sign of an unruptured internal carotid aneurysm is presented and the literature reviewed.

A progressive unexplained optic atrophy with irregular visual field changes should suggest the diagnosis of internal carotid aneurysm. The early diagnosis is established by carotid arteriography.

Abolishing the aneurysm pulsations by internal carotid ligation can lead to complete recovery of visual loss in early cases and moderate to marked improvement in late cases.

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CASE REPORT

Intrinsic Glomerate Astrocytoma of the Cerebral Hemisphere in a Four Year Old Child

Axel K. Olsen, M.D. and Bluitt L. Landers, Jr., M.D.

GLIOMAS IN CHILDREN are located chiefly in the cerebellum and brainstem, and supratentorial neoplasms are largely limited to basal ganglia, optic pathways, or hypothalamic region. Tumors of the hemisphere are rare in this age group and are usually invasive and poorly circumscribed. We present a case of circumscribed astrocytoma of the parietal lobe in a four year old child.

A four year old colored female was brought to the hospital after a generalized convulsion which occurred during sleep. She was unconscious for 15 minutes after the seizure and incontinent of urine. The mother recalled two similar episodes several weeks before, one during sleep and the other while awake. Physical examination and neurologic studies were negative. There was no elevation of temperature. Laboratory studies were within normal limits. Electroencephalogram revealed high voltage, abnormal slow waves in both hemispheres. No seizures were observed while the child was in the hospital. Three months later the patient developed focal seizures for the first time. These started in the left foot and spread to the entire left side. She did not lose consciousness during these attacks and they were not associated with headache or vomiting. Generalized convulsions were also present during sleep. After this episode the child remained seizure-free for three weeks, when both generalizd and focal convulsions recurred. The eyegrounds showed no signs of increased intracranial pressure and no abnormal neurologic findings were present between seizures. Electroencephalogram now revealed paroxysmal bursts of high voltage, slow waves in both parietal and the left rolandic area, with much slower waves in the right parietal area. A pneumoencephalogram taken during this period was interpreted as showing a space-occupying lesion in the right parietal region, compressing the temporal horn of the ventricle. The child was removed from the hospital and was not seen until six months later when she was admitted with focal seizures of the left foot. The mother stated that no convulsions had been noted during the interval. Shortly after admission a left hemiparesis developed and permission for surgery was granted.

On opening the cranium in the right parietal region, the dura was tense and the convolutions flattened. On cortical incision a solid, circumscribed mass with a distinct avascular capsule was encountered 1 cm. beneath the surface. A 4 cm. area was exposed without visualizing the entire tumor. The mass occupied the greater part of the parietal lobe and extended to the walls of the lateral ventricle. It was freed by blunt dissection and removed entirely, leaving the wall of the ventricle intact. Postoperatively, the child moved all extremities, but responded poorly to stimuli. On the eighth postoperative day phlebitis of the right leg developed, and he died on the following day.

Pathologic observations. The surgical specimen consisted of a firm, rubbery, globular mass measuring 7 by 4 by 4 cm. It was relatively avascular and grossly resembled a meningioma. The cut surface bulged to reveal dense fibrous structure with many yellowish necrotic areas. Histologic study demonstrated heavy strands of neuroglial fibers and occasional nuclei forming an incomplete capsule at the periphery of the tumor. Elsewhere, the mass was outlined by collagenous strands derived from blood vessels. The neoplasm was composed of mature astrocytic cells and glial processes, but the architectural pattern was not uniform (figures 1 and 2). The most striking feature was the presence of lobulated areas sharply outlined by compact bands of neuroglial fibers, within which clusters of cells with dark staining small oval nuclei were embedded in dense meshes of glial fibers. The fibers gave a positive reaction with the Holzer and phosphotungstic acid hematoxylin stains. These areas closely resembled the intraventricular glomerate astrocytoma described by Boykin and co-workers.[1] In other locations the structure was more nearly that of a classic astrocytoma, with areas of microcystic degeneration. Here the dense piloid arrangement of processes was replaced by fibrillary and proplasmic astrocytes. Vascularity was not marked in any part of the tumor, but in some foci endothelial and fibrous proliferation of vessel walls was noted. In spite of the benign and encapsulated appearance of the lesion, ganglion cells and myelinated fibers were present deep within the neoplasm in one location. No residual tumor was found at necropsy and histologic examination revealed no invasion of adjacent brain tissue.

From the wards and laboratories of Philadelphia General Hospital, Philadelphia, Pennsylvania.
Read in part before the Philadelphia Neurological Society February 1957.

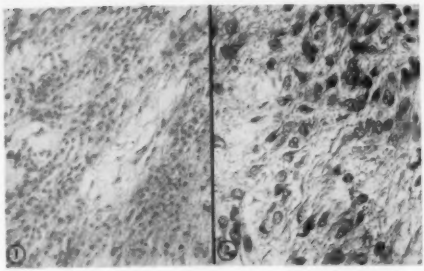

FIG. 1. Glomerate arrangement of cells within dense meshes of glial fibers. An area of microcystic degeneration is present.
FIG. 2. Detail from figure 1 showing cellular and fibrillary structure.

COMMENT

Cushing,[2] in his series of brain tumors in children under 15, listed 106 gliomas, of which 26 (22.4 per cent) were located in the cerebrum. Russell and Ellis[3] reported 12 (21.8 per cent) above the tentorium. The incidence of supratentorial astrocytomas could not be determined from these studies. This form of glial tumor is commonly found in the cerebrum in adults but is apparently rare in this location in children. Miller and co-workers,[4] reviewing 190 supratentorial tumors of all types, found 46 (24 per cent) astrocytomas. Stern[5] reported 19 cases, of which four were astrocytomas. Gliomas occurring above the tentorium in children are described as malignant, invasive, and predominantly involving the basal ganglia or other deep structures. We were able to find only four reports of circumscribed gliomata of the hemisphere. Hagan and Graves[6] described a sharply demarcated glioma in the parietal cortex of a six year old child. The lesion was infiltrating and classified histologically as a glioblastoma. Russell and Ellis[3] reported a well circumscribed solid spherical tumor in the left hemisphere of a full-term stillborn infant It contained many cells in mitosis and was described as a malignant glioma. The same authors reported circumscribed tumors in two other infants but considered them primary sarcoma. Bodian and Lawson,[7] described astrocytoma of the hemisphere in two children, one involving the frontal and the other the temporal lobe. Both of these neoplasms were composed of adult astrocytes but were poorly circumscribed and invasive.

DISCUSSION

The cytologic characteristics of the tumor described in this report are those of an astrocytoma. Its unique architectural arrangement, however, does not conform to the criteria of grade 1 or grade 2 of the classification of astrocytic tumors proposed by Svien, Mablon, and Kernohan[8] and the absence of dedifferentiation and mitosis excludes it from grades 3 and 4. In gross appearance it resembled those tumors previously designated as polar spongioblastoma, rather than the poorly defined cystic type of astrocytoma commonly seen in the cerebral hemispheres. According to Penfield,[9] these tumors are firm, whitish, and well-defined, although not clearly circumscribed, and occurred predominantly in the region of the third ventricle and the optic chiasm. Their cytologic and architectural composition, however, bears little resemblance to the tumor in this case. Except for its size and location, the lesion is more closely allied to the neoplasms reported by Boykin and co-workers[1] as subependymal glomerate astrocytoma. They described such tumors as lobulated, sharply marginated structures projecting into the ventricular cavity by a narrow pedicle based in the subependymal plate. They consist essentially of clusters of small, poorly defined astrocytic nuclei embedded in dense masses of glial fibers. Nuclei are small, oval, uniform in size, and show no mitosis. It is their opinion, however, that this class of tumors originates from astrocytes related to the ventricular wall and, in their experience, do not penetrate brain tissue beyond this area.[10] Since the entire tumor was removed surgically in our case, its point of origin could not be determined. Examination of the necropsy specimen demonstrated its close apposition to the ependymal lining; the operative note, however, definitely stated that the wall of the ventricle was intact. It seems possible that tumors arising from sub-

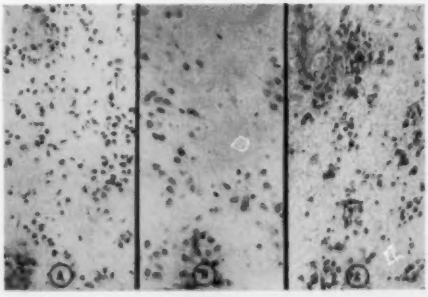

FIG. 3. Comparative fields in three astrocytic tumors characterized by glomerate arrangement. *A*. Circumscribed intrinsic tumor of hemisphere (present case). *B*. Diffuse intrinsic tumor of midbrain. *C*. Subependymal tumor of fourth ventricle.

ependymal astrocytes might, on occasion, reverse their direction of growth. Such a tumor might properly be designated an intrinsic glomerate astrocytoma.

Whatever the source of origin, astrocytic tumors of this type apparently are rarely encountered within the brain substance either in adults or children. We were able to find only one other case among more than 100 astrocytic neoplasms. This tumor, although not circumscribed, presented identical cytologic and architectural characteristics. It had caused diffuse enlargment of the tectum and tegmentum of the midbrain and appeared to originate from the region of a malformed and atresic aqueduct. It is of interest that, while the patient was over 50 at the time of death, the clinical history suggested the lesion had been present since early childhood.

SUMMARY

A clinical pathologic study of a circumscribed astrocytoma of the parietal lobe in a child has been presented. Classification of the tumor has been discussed and the designation of intrinsic glomerate astrocytoma suggested.

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ADDENDUM

James H. Austin, M.D., author of the paper on "Metachromatic Form of Diffuse Cerebral Sclerosis 2. Diagnosis During Life by Isolation of Metachromatic Lipids from Urine" published in the October issue of this journal (Neurology 7:716-723, 1957), has requested that the following comment be added to his material. Its proper place is on page 721, at the end of the first paragraph (. . . . will not be detected by this method.[16]).

> "Further specific information about this important point has been kindly furnished by the authors at the writer's request. The limitation made above, based on the reference cited,[16] now does not necessarily hold. In 1939, the aqueous toluidine blue technic – essential to reveal the renal material – was not routinely applied to frozen sections of kidney. The kidney in this adult case could, therefore, only be regarded as negative in the report at that time."

Neurology

BOOK REVIEWS

Atlas of Tumors of the Nervous System

H. M. Zimmerman, M.D., Martin G. Netsky, M.D., and Leo M. Davidoff, M.D. 1956. Philadelphia, Pa.: Lea and Febiger. 191 pages, 277 illustrations (233 in color). $25.00.

THIS ATTRACTIVE monograph represents the combined efforts of three distinguished authors who are well qualified to speak with authority on their subject—one of them is a pathologist, one a neuropathologist and clinical neurologist, and one a neurosurgeon. Their purpose has been to present the morphologic features, gross and microscopic, of space-occupying lesions of the central and peripheral nervous systems in such a way as to be helpful to interested clinicians and pathologists who may be concerned with the pathologic diagnosis of these lesions.

An extremely large field of lesions is covered, ranging from intracranial gliomas to tumors of the peripheral nerves and autonomic ganglia. These are presented in orderly fashion in logical groupings depending upon the general region of the nervous system or its coverings involved. Not only neoplasms are included, but other lesions which may behave clinically like tumors, such as brain abscess and infective granulomas. Furthermore, there are sections devoted to the general effects of increased intracranial pressure on the brain and of compression on the spinal cord. The classification of gliomas followed in this book is that of Bailey and Cushing, which the authors believe is the most practical, and which employs terms that are familiar everywhere. At the end there is an excellent bibliography, followed by a most useful appendix giving statistical incidence of intracranial tumors and gliomas in two large groups of cases (New Haven Hospital series and Cushing series), staining methods, and synonyms that may be encountered in the literature in association with diagnostic terms used.

In this book, the chief emphasis has been placed on the illustrations. These are numerous, and illustrate well the features that they are supposed to indicate, although some of the color pictures have suffered to some extent in the reproduction process. The text is brief and concise, and supplies the necessary background to the illustrations. It naturally presents the particular views of the authors—and there may be slight differences of opinion concerning some of the details. Be that as it may, there is no doubt of the soundness of the information contained, and those who wish to find out more for themselves can rely on the extensive bibliography.

The authors are to be commended for having gathered together, in a most presentable form, a large amount of information that is now much more readily accessible than it ever has been previously.

E. P. R.

The Early Diagnosis and Treatment of Acoustic Nerve Tumors

J. Lawrence Pool, and Arthur A. Pava. 1957. Springfield, Illinois: Charles C Thomas, Publisher. American Lecture Series, Publication 303. 161 pages. $5.50.

IN A SHORT and easy reading monograph, the authors present the experiences of the surgeons of the New York Neurological Institute in the operative treatment of acoustic nerve tumors. After brief mention of the historic and pathologic aspects of the subject, the statistical data of 122 patients suffering from acoustic neuromas is presented, stressing age, symptoms, signs, and the results of special complications and results of operative excision of these tumors. A short but adequate bibliography is

given and an index is appended.

In the past decade a number of extensive reports on the surgical therapy of acoustic tumors have appeared from the clinics of Dandy, Horrax, Olivecrona, and Jefferson. This review from the New York Neurological Institute seems to indicate that their experience falls in line with the above reports. Although complete removal of the tumor with preservation of the facial nerve is possible in about 20 per cent of cases, a less ideal procedure is carried out in many cases. It is generally agreed that total removal in younger individuals carries no higher a mortality than partial and eventually has a lower risk to life. The facial paralysis which results in most cases, the authors state, can be made less noticeable by hypoglossal anastomosis (in preference to faciospinal accessory) or by plastic procedures. However, the authors believe subtotal or intracapsular extirpation has a place in older individuals. It is interesting to note that if a recurrence does not occur within three years, the patient seems to have a good chance of survival for an indefinite period.

In reviewing this monograph, one notes no radical advances in surgical approaches since Dandy's unilateral incision and complete extirpation of the tumor and capsule. Unquestionably the mortality rate has decreased due to earlier diagnosis and more experienced operators. Unless a radical technical advance is made, Dandy's mortality of 6.5 per cent over an eight-year period seems to be as low as one will attain.

This monograph is recommended to all neurologists and neurosurgeons desirous of reading an up-to-date account of the subject. It is well written, concise, authoritative, and well printed in the Thomas tradition. The numerous illustrations are clear and well selected to amplify the text.

A. E. W.

Functions of Autonomic Transmitters

J. Harold Burn. 1956. Baltimore: Williams & Wilkins Company. 228 pages. $5.00.

This is an extremely readable and informative group of seven essays constituting the Abraham Flexner Lecture Series for 1956, given at Vanderbilt University by the professor of pharmacology of Oxford.

The general topic involves the theory of the humoral transmission of nerve impulses. After a historical review of the relationship of acetylcholine and cardiac muscle, the author presents the detailed experimental evidence for the excitory action and, under some circumstances, inhibitory action of acetylcholine, together with comments on its relationship to the automatic rhythm of the heart. The view that the heart beat is myogenic is of critical importance in all hypotheses involving this system and serves to indicate that the nerve fibers, so abundantly present in the auricles, do not establish a basic rhythm but simply alter it.

The author's view that rhythmic activity of the heart is maintained by local synthesis of acetylcholine was further tested in rhythmic movement of cilia. It was found that in the non-innervated gill-plates of the mussel, *mytilus edulis*, the ciliary movement is controlled by the local production of acetylcholine and that enzymes capable of synthesizing and of destroying it are also present.

There follows a review of experimental work illustrating the distinction between the action of norepinephrine and epinephrine, together with a note on their clinical usefulness. A chapter on the common properties of drugs presents experimental evidence that groups of drugs (including chlorpromazine and others) exert many characteristic effects by their tendency to depress the action of acetylcholine in the tissues.

To laboratory workers the discussion of the supersensitivity and subsensitivity of denervated structures will be stimulating, for numerous paradoxes arise which compel a distinction between the role of the nervous system and the purely local chemical reactions in the organs concerned.

A chapter written in a lighter vein, "Our National Drugs—Alcohol and Nicotine," brings the book to a close. This monograph is noteworthy for the straightforward presentation of experimental material, the emphasis on synthesis, and the comprehensive integration of data observed in a comparative animal series from mollusks through amphibians to man.

A. R. V.

The Riddle of Stuttering

C. S. Bluemel. 1957. Danville, Illinois: The Interstate Publishing Company. 142 pages. $3.50, paper bound $1.50.

DESPITE the title of the book, the author uses and recommends the term "stammering" to replace the term "stuttering" for pathologically disorganized speech and recommends the term "stuttering" for the nonfluency which is not pathologic. This is contrary to common American usage.

These two primary components of his riddle are analyzed symptomatically by the author as nonorganized, nonfluent speech (stuttering) and disorganized speech with marked blocking (stammering). Three secondary symptoms are an effort phase in attempts to force the block, conditioning to expect trouble in certain situations, and obsessive anxiety in relation to speech. Much of the book is taken up with a theory of "stammering" which proposes that "stutterers" are of diffident, indecisive, passive-submissive personality make-up and possess poor neuromuscular coordination and poorly organized (nonfluent) speech; that when such persons are subjected to stress, their speech becomes disorganized and they block; and that the effort phase, conditioning phase, and obsessive-phobic phase develop progressively, if stress continues, and complete the syndrome of "stammering." In therapy, the author recommends establishing good patterns of "verbal thinking."

In the reviewer's opinion, the theory presented is supported chiefly by anecdotal evidence and analogies to other conditions. Even in such a small book there is much reading to glean the useful information.

J. R. B.

Progress in Neurobiology

Edited by J. Ariens Kappers. 1956. Princeton, New Jersey: Van Nostrand Co. 384 pages. $10.50.

THIS BOOK presents the addresses and papers delivered at the first international meeting of neurobiologists, held in the department of anatomy and embryology at the University of Gronigen, the Netherlands. Dedicated to the memory of Ludwig Edinger, the collected essays have a pronounced morphologic emphasis and the reviewer wishes to alert all those who are interested in the structure of the nervous system to the mine of information which this treatise holds for them.

The first section is a symposium on the morphology and physiology of the synapse. The second section is a symposium on the cerebrospinal fluid and some paraventricular organs. This series of ten papers presents commendable studies in comparative neurology on the saccus vasculosus, pineal organs, paraphysis, and walls of the third ventricle.

The next section, in keeping with present day orientation, deals with the morphology and physiology of the reticular substance in the brain. There is a wholesome respect here for the neuroanatomic realities; the morphologist knows that the demonstrated neuron systems are not to be too lightly brushed aside by the introduction of a diffuse network. This attitude is summarized in the statement of Elizabeth Crosby when she remarks that the effects of lesions in the midbrain "depend only in part—and perhaps to a decidedly limited extent—on the involvement of the multisynaptic reticular paths."

The papers are written in either English, French, or German, and each is followed by a verbatim discussion. The book can be recommended to all both for the solidity of its material and as an expression of the fertility of modern basic neurology.

A. R. V.

Management of the Patient with Headache

Perry S. MacNeal, M.D., F.A.C.P., Bernard J. Alpers, M.D., Sc.D. (Med.), F.A.C.P., and William R. O'Brien, M.D., F.A.P.A. 1957. Philadelphia: Lea and Febiger. 145 pages. $3.50.

DESIGNED as a guide for all physicians concerned with the management of headache (and few are not), this small volume represents the integrated effort of an internist, a neurologist, and a psychiatrist to formulate some ground rules of diagnosis and treatment based on contemporary thinking in their respective specialties. The authors adopt the prevalent view that most headache falls into one of three categories: those caused by organic intracranial disease, those of a purely

psychogenic origin, and those dependent upon intra- and extracranial vascular mechanisms. It is obviously impossible in a book of this scope to deal with the organic headaches in any detail, but appropriate suggestions are given for screening the organic from the far more numerous psychogenic and vascular headaches.

The management of this latter group of "functional" headaches, a term not used by the authors, forms the main theme of the work. Many practical instructions for psychotherapy of such patients are made which should be useful to physicians not expert in this field. Drug therapy of headache is well presented.

Among the virtues of the book is the emphasis on history taking in the chapter on "Diagnostic Techniques." From the theoretical standpoint, however, the book is based on orthodox Freudian doctrine and takes on authoritative, not to say, dogmatic, tone on matters that are quite controversial. Not everyone with experience in the therapy of headache will agree that migraine is primarily and fundamentally a psychogenic disorder nor that the variety of vasodilating cephalgia, sometimes known as "histamine cephalgia," is allergic in origin.

R. B. R.

Hypothalamic-Hypophysial Interrelationships

William S. Fields, M.D., Roger Guillemin, M.D., and Charles A. Carton, M.D. 1956. Springfield, Illinois: Charles C Thomas, Publisher. 156 pages. $4.75.

THIS IS AN ACCOUNT of a symposium given in 1955 in Houston, Texas, and presents a group of essays by various authors. While a work of this kind cannot possibly have the unity of a planned monograph, nevertheless these papers are especially valuable if they are read after a comprehensive presentation of background material such as "Neural Control of the Pituitary Gland," by G. W. Harris, which was previously reviewed in *Neurology*.

Neural pathways to the hypophysis is discussed by John D. Green, and neurosecretion by W. P. Hild. G. W. Harris presents an important summary on the hypothalamic control of the anterior lobe. Introducing physiologic considerations is the paper by R. Guillemin on the production of pituitary hormones, followed by papers of Stein and Mirsky on the effect of stress, of P. Gloor on telencephalic influences, and of Pool, Clark, Hudson, and Lombardo on the hormonal responses to electric stimulation in the subfrontal parts of the brain. A chapter on hypothalamic-hypophysial dysfunction in man by Spurr and Stribling, followed by a general discussion and summary, brings the work to a close.

A. R. V.

Hirnabszess

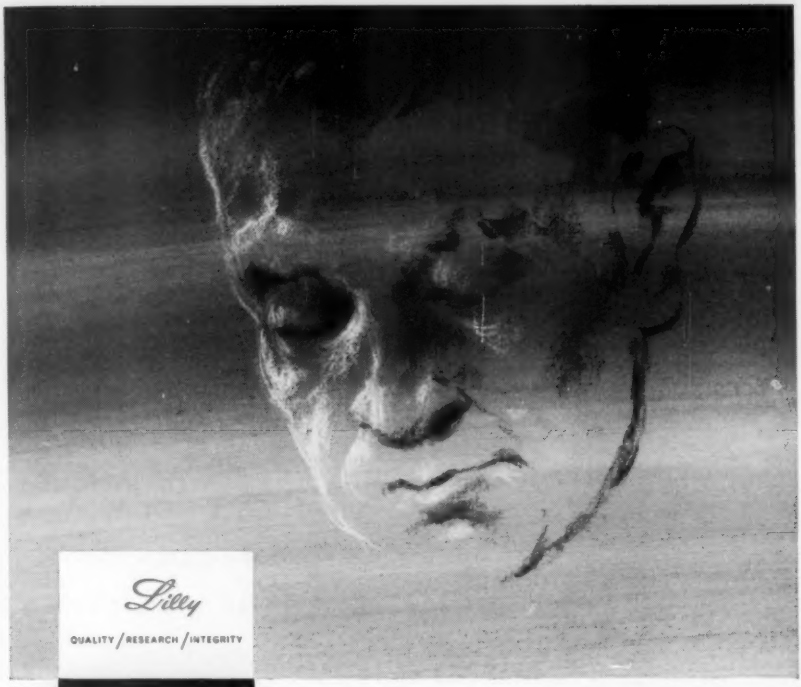
Gerhard Weber. Stuttgart: Georg Thieme. 188 pages. $7.10.

THIS SHORT MONOGRAPH from the neurosurgical clinic of Zurich covers much more than its title suggests. It presents the experiences of the author with all types of infection within the intracranial cavity. In fact, more than half of the book deals with the symptoms, signs, and diagnosis of infection of the skull, venous sinuses, and epidural, subdural, and subarachnoid spaces. The last 75 pages are concerned with brain abscess proper.

The recent literature is well reviewed with a good bibliography. No illustrations are presented.

Because of the rapid and changing development of antibiotic therapy, it is quite understandable how any book on the subject of infections is out-of-date by the time it is published, and this monograph is no exception. However, the principles of medical and surgical therapy remain valid. Anyone desiring to trace the trends in the current world literature on infections of the cranial contents will find this a very valuable source book.

A. E. W.



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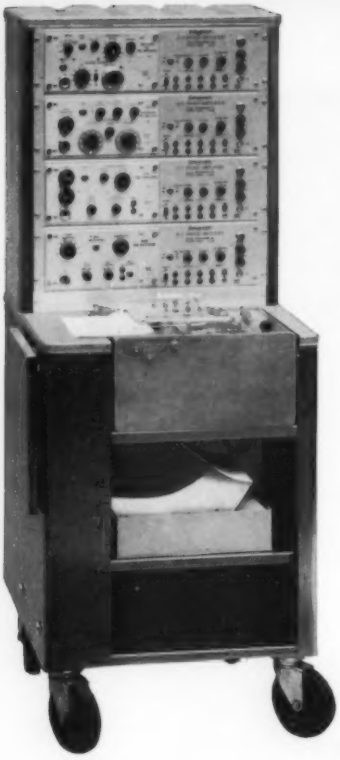

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Lerner, P. F.: Kemadrin, a New Drug for Treatment of Parkinsonian Disease, J. Nerv. & Ment. Dis. 123:79 (Jan.) 1956.

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1. Fazekas, J.F., et al.: J.A.M.A. *161*:46 (May 5) 1956.

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NEWSLETTER

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NOVEMBER 1957

Geomedical Conference Held in Brussels

The first international geomedical conference on diseases of the nervous system was held (July 23) as part of the program of the Sixth International Neurological Congress in Brussels. The purpose of the conference was rooted in the thesis that a collaborative study of environmental and genetic factors in particular geographic areas might supply clues for the predisposition to diseases of the nervous system in certain populations, which could be best followed by comparing the results of population statistics for different parts of the world; 46 scientists from 16 countries attended the conference. After discussing several mortality, necropsy, morbidity, and population surveys now underway or contemplated,[1] the conferees agreed on the need for international cooperation for the establishment of uniform criteria for the analysis of any data to be collected. Also discussed was a suggestion by Roland P. Mackay for sending a team of neurologists and epidemiologists into selected isolated areas for intensive study of a local population[2].... The conferees in Brussels appointed an interim committee (under the chairmanship of Leonard T. Kurland of the National Institute of Neurological Diseases and Blindness) to develop uniform survey criteria which would be suitable for selected geographic areas. If these objectives can be attained, plans will be proposed for a symposium on geomedical research in neurologic disorders at the next international neurological congress, to be held in Rome (1961).

International M. S. Group Holds Second Meeting

On July 24 the corresponding members of the International Panel of the National Multiple Sclerosis Society (Headquarters: 257 Fourth Avenue, New York City) held its second meeting in the halls of the Palais d'Egmont in Brussels, in conjunction with the First International Congress of Neurological Sciences. It was a dinner meeting, organized by the society's medical and research director, Thomas L. Willmon. After dinner, the program was opened by the president of the panel, Prof. G. H. Monrad-Krohn (Oslo), who described briefly the panel's activities since 1953. The election of officers followed and H. Houston Merritt was unanimously elected president of the panel, succeeding Monrad-Krohn. A more de-

[1]The value of necropsy studies was discussed by Schaltenbrand (Wurzburg), Geordi (Basel), Henner (Prague), and Chandy (Vellore).

[2]Discussions on local surveys were conducted by Okinaka (Japan), Luthy (Zurich), Broman (Goteberg), and Rodriquez-Arias (Barcelona).

tailed account of the society's activities, past and present, was given by Dr. Willmon, who highlighted the excellent cooperation of the Bio-Sciences Information Exchange with the society in preparing the areas covered in MS research.... Also present at the dinner and the meeting was Miss Sylvia Lawry, founder and executive director of the society.

Vienna Neurological Institute Celebrates its 75th Anniversary A sequel of the First International Congress of Neurological Sciences (Brussels, July 21-28) was the celebration (July 31-August 1) of the 75th anniversary of the Neurologischen Institut at the University of Vienna, founded in 1882 by Heinrich Obersteiner (1847-1922). The story of the Vienna Institute is a landmark in neurologic leadership, for it was the first institute in Europe dedicated to studies on the anatomy and pathology of the nervous system, and, as such, served as a prototype for institutes that were organized later.... For the first day of the meeting, about 60 neurologists and neurologic scientists from some 16 different nations assembled in Vienna to pay tribute on behalf of their respective countries to the inaugural sessions of this meeting, which also highlighted three special presentations. The first was given by Prof. Leopold Schonbauer who called to mind, in addition to Obersteiner, the Institute's great scientific leaders: Otto Marburg (1874-1948),[3] Otto Gagel, and finally Hans Hoff, the Institute's director since 1949, who is also professor of neurology and psychiatry at the University of Vienna. The second presentation, by Ludo van Bogaert, set forth today's concepts in neuropathology as they relate to concepts initiated by the neurologic institute in Vienna. The third presentation, made by Prof. Hoff himself, outlined the future of neuropathologic research at the institute. The morning inaugural sessions were followed by a luncheon at the Palais Auerspergh, a reception at the town hall, and a gala concert in a setting of a fine collection of 18th century prints and etchings, excelled only perhaps by the collections in Florence and the Louvre. A genial evening in the friendly village of Grinsingen, one of the "Heurige" or new wine gardens, ended the day. The second day was devoted to a tour of the institute, including a series of clinicoanatomic demonstrations by Associate Professor Franz Seitelberger and his staff.... Among AAN members in Vienna from the U. S. A. were Kenneth Abbott, William Caveness, Konstantin Scharenberg, and Charles M. Poser.

Symposium on Curare Held in Rio de Janeiro An international symposium on curare and curare-like substances was held in Rio de Janeiro (Aug. 5-17). Approximately 200 scientists from the United States, Britain, France, Italy, Brazil, Argentina, Peru, Venezuela, Colombia, Spain, and Chile attended.

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[3]With the aid of Bernard Sachs and the Rockefeller Foundation, Marburg came to New York during World War II where he resumed his investigations in the laboratories of the Mount Sinai Hospital, the Montefiore Hospital, and the Neurological Institute, becoming clinical professor of neurology at Columbia University.

Forty communications were presented, dealing with these compounds in their ethnographic, botanical, chemical-physio-pharmacodynamic, and clinical aspects. Among the papers receiving special attention were those by J. Vellard (Lima), R. L. Froes (Belem), Paul Karrer (Zurich), C. Hejmans (Gant), V. Boekelheide (Rochester), D. Bovet (Rome), C. Chagas (Rio de Janeiro), D. Taylor (Los Angeles), and F. F. Foldes (Pittsburgh).... The symposium was sponsored by the President of the United States of Brazil and organized under the auspices of UNESCO, the Brazilian Research Council, the Brazilian Academy of Sciences, and the University of Brazil. On the executive committee of the symposium were, Paulo B. Carneiro of the Brazilian delegation at UNESCO (Paris); Arthur Moses, president of the Brazilian Academy of Sciences; Carlos Chagas of the University of Brazil; and Daniel Bovet of the Superior Institute of Health (Rome).

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New York Meetings in December Promise Large Attendance A large gathering is expected at the yearly round of neurologic meetings to be held in New York in mid-December. The first is the annual meeting of the American League Against Epilepsy at the Roosevelt Hotel, December 12. The league program includes symposia on types of status epilepticus, physiology, and treatment; toxic reactions to anticonvulsant drugs and their control; medical and psychologic aspects of psychomotor and temporal lobe epilepsy in adults and children. Also there will be a limited number of free communications. Questions relative to the program should be submitted to Dr. Gilbert H. Glaser, Section of Neurology, Yale University School of Medicine, New Haven 11, Conn..... Another annual meeting is the one of the Association for Research in Nervous and Mental Disease (Dec. 13-14), also to be held at the Roosevelt Hotel. The topic to be discussed is "The Effect of Pharmacologic Agents on the Nervous System." Chairman of the 1957 ARNMD Commission is Francis J. Braceland and the secretary-treasurer of the Association is Rollo J. Masselink, 700 West 168th St., New York 32, New York.... The last meeting of the series is the annual examinations of the American Board of Psychiatry and Neurology (Dec. 16-17), to be held at the New York State Psychiatric Institute and the Neurological Institute.

Masland Joins NINDB Richard L. Masland has been appointed assistant director of the National Institute of Neurological Diseases and Blindness in Bethesda. Before coming to NINDB (Sept. 18) Dr. Masland was professor of psychiatry and neurology (in charge of neurology) at the Bowman Gray School of Medicine. A Philadelphian by birth, he was graduated from Haverford College (1931) and the University of Pennsylvania School of Medicine (1935). After a two-year internship at the Pennsylvania Hospital in Philadelphia, his neurologic career began and continued a steady climb to distinction in the role of clinician, teacher,

author, and researcher in both neurology and clinical neurophysiology. At the University of Pennsylvania he was appointed fellow in neurology (1938-1939) and associate in neurology (1940-1946), while at the Pennsylvania Hospital his title was assistant neurologist (1939-1946). During the war Dr. Masland served as director of the department of physiology, School of Aviation Medicine at Randolph Field, Texas. His connection with the Bowman Gray School of Medicine began in 1947 as assistant professor, rising to full professor in 1955. A fellow of the American Academy of Neurology since 1949, he was president of the American League Against Epilepsy in 1954. His society membership also includes the American Neurological Association, the American Electroencephalographic Society, the American Medical Association, and other national medical societies.... In July 1955 Dr. Masland obtained leave of absence from Bowman Gray to become research director of the National Association for Retarded Children to direct a nationwide survey of research facilities and opportunities in the field of mental retardation. He also comes to NINDB as a former part-time colleague, having served previously as consultant to the institute and a member of its training grants committee.

Auth Becomes VA Neurology Chief Thomas L. Auth has been appointed temporary chief of the neurology division, Psychiatry and Neurology Service, of the Veterans Administration Central office, Washington, D. C. Succeeding Benedict Nagler who occupied the post since 1953, Dr. Auth assumed his new duties September 9, 1957. Born in Springfield, Mass., he received his general medical training at the Georgetown University School of Medicine and the D. C. General Hospital. His training in neurology was at the Cushing VA Hospital and the Georgetown University Hospital under Francis M. Forster. Prior to becoming the VA neurology chief, Dr. Auth was assistant chief of the neurology service at the Mt. Alto VA Hospital and assistant professor of neurology at Georgetown.... Dr. Nagler now is superintendent of the Lynchburg Training School and Hospital, Colony, Virginia.

Briefs The symposium of the Houston Neurological Society on the "Pathogenesis and Treatment of Parkinsonism" will be held on March 13 and 14, 1958, and not on March 16 as stated in the August Newsletter.... The proceedings of the Second International Congress of Neuropathology (London, 1955) have been published and may be purchased from Excerpta Medica Foundation, 111, Kalverstraat, Amsterdam, The Netherlands. The editor is W. H. McMenemey.

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references (1) Rodriguez-Gomez, M.; Valdes-Rodriguez, A., and Drew, A. L.: J.A.M.A. 160:752 (Mar. 3) 1956. (2) Settel, E.: Am. Pract. & Digest Treat. 8:443 (March) 1957. (3) Abrahamsen, E. H., and Baird, H. W., III: J.A.M.A. 160:749 (Mar. 3) 1956. (4) Millichap, J. G., and Hadra, R.: Neurology 6:843 (December) 1956.

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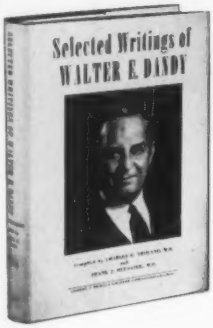

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